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SYNDROMES ASSOCIATED WITH "ALLERGIC" VASCULITIS*

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VASCULITIS denotes inflammation within the walls of blood vessels; it develops as a nonspecific reaction to various stimuli, including trauma, infection, thrombosis, embolization and hypersensitivity; it is also seen adjacent to some tumors, in eruptive xanthomatoses and in severe hypertensive states. In the absence of pathological evidence that active vasculitis is secondary to some other disorder, the possibility of an allergic origin must be seriously considered. Proof of allergic etiology in a given case, however, is difficult because of the lack of suitable immunologic technic.

There is ample experimental and clinical evidence that small blood vessels may be involved in allergic reactions, and a growing realization that many clinical syndromes of uncertain etiology may be of allergic origin. The various clinical manifestations of allergic vasculitis have not been clearly delineated, however, because clinicians have not been aware of the occurrence of vasculitis in many common syndromes, and pathologists have had little opportunity of studying tissues from patients with allergic vasculitis, except in fatal cases. Consequently, the impression has grown that this reaction carries a poor prognosis.

Increasing use of biopsies of skin and muscle as diagnostic procedures in patients with obscure diseases has revealed that vasculitis is much more common than had previously been realized, and frequently associated with obvious allergic reactions. We have undertaken a study of a number of these cases to record the diversity of symptoms that may develop as a sequel to vasculitis. We have chosen to use the term "allergic" vasculitis to indicate the likelihood that an allergic mechanism is involved, but retain the quotations about the word "allergic" to indicate that proof of this factor is still lacking.

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REVIEW OF THE LITERATURE

Opie[1] described vasculitis in the Arthus phenomenon. Gruber[2] suggested that hypersensitivity to foreign substances might be involved in periarteritis nodosa. Swift, Derick and Hitchcock[3] suggested that rheumatic fever (in which vasculitis occurs) could be a manifestation of hypersensitivity to streptococci. Klinge[4] extended the list of clinical conditions that may be caused by hypersensitivity to include rheumatic disease, dermatomyositis, malignant nephrosclerosis, thromboangiitis obliterans, certain nephritides and subacute bacterial endocarditis. Clark and Kaplan[5] demonstrated the presence of vasculitis in serum sickness in man, and Hawn and Janeway[6] recorded similar pathological findings in experimental serum disease. Baehr, Klemperer and Schifrin[7] noted the diffuse vascular changes that occur in disseminated lupus erythematosus, and described the typical changes that occur in the kidneys in this disease. Klemperer, Pollack and Baehr[8] later elaborated on the pathologic changes of disseminated lupus erythematosus, pointing out that in this disease there was a disturbance of the collagen tissues throughout the body and that the necrotizing vascular changes were only one expression of this collagen disturbance. They stressed the fact that similar changes could be produced experimentally in the absence of hypersensitivity and indicated that the presence of necrotizing vasculitis and collagen degeneration did not necessarily indicate that hypersensitivity played a part in their production. Rich and Rich and Gregory noted the association of periarteritis nodosa with serum sickness and sulfonamide therapy[9,10] and iodine therapy,[11] and with his co-workers Rich has done much to clarify the subject of hypersensitivity in disease.[12] Zeek[13] recognized that various pathologic disorders were being erroneously called "periarteritis nodosa"; she proposed that the generic term "necrotizing angiitis" be used to designate vascular lesions characterized by fibrinoid necrosis and inflammatory reactions involving all three coats of the vascular wall; in her

classification, five types of necrotizing angiitis could be differentiated (hypersensitivity angiitis, allergic granulomatous angiitis, rheumatic arteritis, periarteritis nodosa and temporal arteritis). In her patients with "hypersensitivity angiitis" there was a rapidly progressive downhill course, death inevitably occurring within a month. Churg and Strauss[14] discussed the pathological findings in a fatal syndrome with allergic vasculitis and granulomatosis. A similar disorder characterized pathologically by necrotizing granulomatous lesions of the respiratory tract, generalized arteritis and focal glomerulitis was described by Klinger[15] and later by Wegener.[16]

TABLE 1. *Clinical Findings in 30 Patients with "Allergic" Vasculitis.*

CLINICAL FINDING	"ID" REACTION		URTICARIA & ANGIOEDEMA		VASCULAR ANAPHYLACTOID PURPURA								ERYTHEMA NODOSUM		
	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8	CASE 9	CASE 10	CASE 11	CASE 12	CASE 13	CASE 14	CASE 15
Past history of allergy															
Allergic factor at onset	+	+			+	+	+		+	+	+	+	+		+
Symptoms:															
Arthralgias							+	+	+				+		
Purpura					+	+	+	+	+	+	+	+			
Edema					+	+							+		
Fever						+	+		+	+			+		+
Weight loss						+	+		+					+	
Pleurisy or pneumonitis							+							+	+
Subcutaneous nodules													+	+	+
Dermatitis	+	+													
Muscle tenderness or weakness															
Urticaria			+	+	+			+							
Neuritic pain or paresthesias															
Gastrointestinal bleeding						+	+								
Laboratory findings:															
Anemia						+	+		+	+				+	
Leukocytosis					+	+	+				+				
Eosinophilia	±	+++		+		±			+	±		±		±	+
Elevated sedimentation rate					+	+			+++	+++			+	+	+
Abnormal serum protein						+	+		+		+				+
Hematuria & albuminuria						+	+	+	+		+				
Renal failure						+	+		+						
Hepatic failure															
Steroid therapy	+	+	+		+			+	+				+	+	+
Prognosis:															
Complete recovery	+	+			+					+	+	+	+	+	+
On maintenance or intermittent steroid treatment			+					+							
Residual disease							+								
Death						+			+						

CLINICAL MATERIAL

We have had the opportunity of studying 30 patients (19 men and 11 women), in each of whom a

diagnosis of "allergic" vasculitis was established pathologically during life by skin or muscle biopsy or both. In none of these cases has it been possible through continued observation or post-mortem study to establish a diagnosis of disseminated lupus erythematosus or periarteritis nodosa, disorders often producing similar symptoms and pathological findings but not included in this study because their clinical characteristics are well known.

We believe that these patients represent a group in whom vascular changes result from an allergic reaction within the vessel walls. The symptoms and signs for the most part may be explained on the basis of the vascular abnormalities present. Treatment with adrenal steroids has been highly effective. On the whole, the prognosis of this disorder is favorable unless there is renal involvement, and especially if an underlying allergic factor can be recognized and

TABLE 1 *(Concluded).*

CLINICAL FINDING	DERMATOMYOSITIS			VASCULITIC EDEMA			UNCLASSIFIED SYNDROMES									TOTALS
	CASE 16	CASE 17	CASE 18	CASE 19	CASE 20	CASE 21	CASE 22	CASE 23	CASE 24	CASE 25	CASE 26	CASE 27	CASE 28	CASE 29	CASE 30	
Past history of allergy	+							+							+	3
Allergic factor at onset	+	+	+						+	+			+	+		18
Symptoms:																
Arthralgias		+	+					+		+	+	+	+	+	+	13
Purpura							+	+	+			+	+			13
Edema	+	+	+	+	+	+		+						+		11
Fever								+	+		+		+		+	11
Weight loss									+	+				+	+	8
Pleurisy or pneumonitis		+							+			+			+	7
Subcutaneous nodules									+	+				+		6
Dermatitis	+	+			+								+			6
Muscle tenderness or weakness	+	+	+					+	+		+					6
Urticaria															+	5
Neuritic pain or paresthesias				+		+		+		+						4
Gastrointestinal bleeding															+	3
Laboratory findings:																
Anemia											+	+	+	+	+	10
Leukocytosis										+	+					6
Eosinophilia		±	±	+				+++			±			±	+++	16
Elevated sedimentation rate		+	+				+	+	+	+++	+++	+++	+++	+++		18
Abnormal serum protein				±		+		+	+			+				10
Hematuria & albuminuria			+								+	+	+	+	+	11
Renal failure												+	+	+		6
Hepatic failure									+						+	2
Steroid therapy	+	+	+	+	+	+		+	+	+	+					19
Prognosis:																
Complete recovery	+	+	+				+			+					+	15
On maintenance or intermittent steroid treatment				+	+	+		+			+					7
Residual disease									+			+				3
Death													+	+		4

eliminated. In some cases a healed stage of vasculitis with arteriolar sclerosis has been demonstrated.

Etiology

Only 3 of the patients gave a history of previous allergic disease. Five had had rheumatoid arthritis or rheumatic fever. In 18 of the 30 patients, however, factors present at the onset strongly suggested that an allergic mechanism was responsible for the clinical disorder (Table 1). Clear-cut drug allergies were evident in 7 patients (Cases 2, 5, 12, 17, 24, 25 and 28).* Reactions to penicillin occurred in 3 (Cases 6, 7 and 18). Two patients (Cases 1 and 11) had reactions to medication but it was not clear whether it was an antibiotic or other drug, since both were given; in 3 others (Cases 9, 13 and 15) it was not clear whether an infection or the medication given to control it was responsible. In 2 (Cases 11 and 28) an infection seemed to be the primary cause. In 1 (Case 16) a tumor seemed to be serving as an antigen. (We have reported a similar case,[17] and a number of others have been recorded in the literature.[18]) In 12 patients there was no clear relation of the symptoms to possible antigens. No other etiologic factors were apparent in these patients.

FIGURE 1. *Skin Biopsy in Case 5 (Acute Vasculitis), Showing a Longitudinal Section of a Small, Patent Vessel Deep in the Corium, with Swollen but Intact Endothelial Cells and a Rich Infiltration of the Wall with an Inflammatory Exudate.*

Pathology

"Allergic" vasculitis consists of inflammation with fibrinoid necrosis involving all three coats of vessel walls (arterial and venous). Arterioles and capillaries of the deeper layers of the corium are principally involved in the vasculitic process. The degree of involvement in our cases varied, from case to case and in an individual case from vessel to vessel, in intensity, age and extent of reaction. Vessel walls were commonly saturated with fluid, fibrin or leukocytes, and at times there were necrosis and lysis, with thrombosis, collapse or complete destruction of the vessels (Fig. 1 and 2). Other vessels seemed patent and reasonably intact. Vasculitis in the skin was associated with edema and deposition of fibrin, and at times with escape of erythrocytes and leukocytes into the tissues. A healed stage of vasculitis was encountered in 3 patients (Cases 2, 19 and 20); in these there was perivascular cuffing with lymphocytes (Fig. 3) or recanalization (Fig. 4). Vasculitis in muscles was associated with varying forms of degeneration, necrosis, lysis and nonsuppurative myositis (Fig. 5). Vasculitis in the kidney was often manifested as glomerulitis (Fig. 6).

Symptoms and Signs

The manifestations of vasculitis and the frequency of their occurrence in the 30 patients are summarized in Table 1.

Arthralgia. Pain occurred in and around the joints; moderate redness and swelling of the joints were common. The changes were reversible as in rheumatic fever and serum sickness, leaving no residual joint deformity when the reaction subsided.

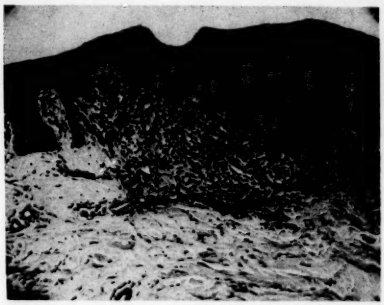

FIGURE 2. *Skin Biopsy in Case 20 (Acute Vasculitis). A small vessel high in the corium is the focal point of an acute inflammatory reaction characterized by a lymphocytic cellular exudate, occlusion of its lumen and saturation of its walls with fibrin.*

Purpura. Vascular purpura occurred principally in areas where physical factors such as dependency, local pressure or scratching enhanced the escape of red cells from the damaged vessels. Only one patient had thrombocytopenia (Case 12), and in this case vasculitis was present as well. The occasional association of thrombocytopenic and anaphylactoid purpura has been pointed out by Stefanini and Mednicoff.[19] Kriedberg, Dameshek and Latorocca[20] have recently speculated upon the allergic nature of vascular purpura.

Edema. This was the primary complaint in 3 patients and was a significant finding in 9 others. It was most frequently present in the legs, but also oc-

*Numbers in parentheses refer to cases outlined in Table 1 and abstracted at the end of this paper.

curred on the hands and face. The edema usually disappeared promptly during steroid therapy.

The fact that edema occurs as the result of vasculitis and as an early manifestation of scleroderma and dermatomyositis led us to perform skin and muscle biopsies upon the 3 patients (Cases 19, 20 and 21) with primary edema of unknown cause. When vasculitis was demonstrated in the microscopical sections in each case, steroid therapy was given, and prompt diuresis with loss of edema ensued. There has been no subsequent evidence of dermatomyositis or scleroderma in these cases.

FIGURE 3. *Skin Biopsy in Case 20 Two Months after Institution of Steroid Therapy (Healed Vasculitis).*
Small vessels in the corium show a narrow border of lymphocytes and collagenous connective tissue. There are no signs of acute inflammation.

Fever. As a general rule, fever when present was low grade and remittent, the temperature rarely rising over 101°F., except in the most severe cases.

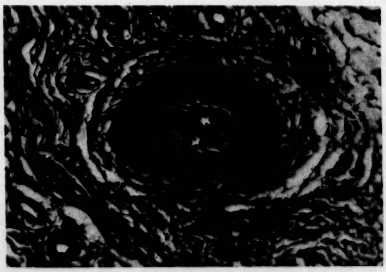

FIGURE 4. *Skin Biopsy Taken Six Months after the Institution of Steroid Therapy in Case 19 (Healed Vasculitis).*
A small artery in the corium shows intimal sclerosis, thrombosis, organization, recanalization, hyperplasia of the muscular media, and an increase in capillaries and collagen in the adventitia.

Spontaneous remissions were common, and the fever responded promptly to cortisone therapy in 7 cases.

Weight loss. Marked, rapid weight loss occurred in several patients with "allergic" vasculitis. In a few cases fever was associated, and the weight loss may have represented a response to an increased

FIGURE 5. *Muscle Biopsy in Case 16, Showing a Rich Lymphocytic Infiltration in the Adventitia of a Small Blood Vessel.*

metabolism. Weight gain occurred regularly when spontaneous or induced remissions occurred.

Pleurisy or pneumonitis. Two patients (Cases 14 and 15) had pneumonitis or nodular changes in the lung parenchyma due to sarcoidosis; 2 others (Cases 7 and 30) had pleural effusions as a phase of the ill-

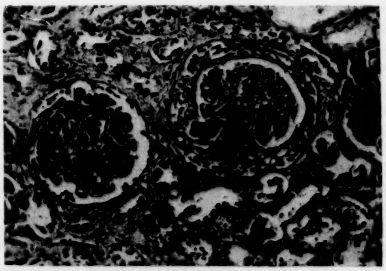

FIGURE 6. *Section from the Kidney at Autopsy in Case 6 (Glomerulitis).*
Two of many glomeruli are involved in a subacute proliferative inflammatory reaction, with changes in both tuft and capsule.

ness; 2 (Cases 24 and 27) had diffuse pneumonitis; it is assumed that this may have been associated with vasculitis of the lung; this phase of "allergic" vasculitis may be associated with glomerulitis and renal failure (as in Case 27), and in these cases the prognosis is poor.[16]

Subcutaneous nodules. Three patients had findings typical of erythema nodosum. In 1 (Case 26) nodules first appeared on the posterior thorax, and in another (Case 25) there were nodules on the forearms after drug administration. Still another patient (Case 29) had nodules that appeared and disap-

peared on the extremities over a period of four years. Nodules regularly disappeared under treatment.

Dermatitis. In 2 patients (Cases 1 and 2) a generalized dermatitis followed local application of a medicated ointment; the positive biopsies were taken of lesions distant from the primary foci. This is the so-called "sensitization" or "id" reaction. Three patients (Cases 16, 17 and 18) showed erythematous, scaling or vesicular lesions, principally on the face, chest and extremities, and associated muscle weakness that in each case proved on biopsy to be due to necrosis of muscle tissue with vasculitis, thus permitting the diagnosis of dermatomyositis to be made. All 3 of these patients also had marked edema, and all responded well to steroids. Another patient (Case 20) had a localized dermatitis in combination with severe edema, both of which responded to steroids.

Muscle tenderness or weakness. Microscopical abnormalities of muscle (necrosis and nonspecific myositis) were noted in 7 patients (14 muscle biopsies were performed). In 3 of these, as noted above, the diagnosis of dermatomyositis was entertained. In another patient (Case 26) the muscle changes were associated with recurrent subcutaneous nodules. In still another (Case 23) there were fever, purpura, ascites, eosinophilia and loss of sensory perception. In Case 24 pneumonitis and hepatitis were associated with the myositis.

Urticaria. Vasculitis was found in 1 patient with simple, uncomplicated urticaria (Case 4) and in another with urticaria and angioneurotic edema (Case 3). In other patients with urticaria not included here biopsies have had negative results, so that the significance of the finding of vasculitis in urticaria is not immediately apparent. Urticaria is a symptom in disseminated lupus erythematosus, but there was no reason to suspect this disease in any of our cases. In 2 patients urticaria was associated with purpura (Cases 5 and 8), and in 1, hives regularly heralded the development of recurrent episodes of acute arthralgia (Case 30).

Neuritic pain or paresthesias. Peripheral neuritis is common in periarteritis nodosa, probably because the nutrition of the involved peripheral nerves is impaired by the vascular disease. The same mechanism probably explains this change in the 4 cases in this series in which this was a principal complaint.

Gastrointestinal bleeding. In vascular purpura, microscopical or gross bleeding into the gastrointestinal tract is not uncommon. In 2 of our patients bleeding from the gastrointestinal tract was associated with purpura (Cases 6 and 7); 1 of these had oral and rectal ulcers, and the other a large gastric ulcer. Another patient had a bleeding duodenal ulcer (Case 30).

Laboratory Observations

Red-Cell Count and Hemoglobin

Anemia occurred in patients with uremia and, of course, after gastrointestinal hemorrhage, but was evident in only 4 other patients (Cases 10, 14, 26 and 30), 1 with chronic infection, 1 with sarcoidosis and 2 with severe, generalized manifestations of vasculitis.

White-Cell Count

Leukocytosis (white-cell count over 12,000) was present in only 6 patients. Leukopenia (count less than 5000) did not occur.

Eosinophils

Eosinophilia (4 per cent or more) was present in 16 patients, but in 9 of these there were only 4 or 5 per cent eosinophils; 4 had counts between 6 and 10 per cent, and 3 between 19 and 57 per cent.

Sedimentation Rate

The sedimentation rate was elevated (above 30 mm. per hour by the Westergren method) in 18 patients, and in 7 of these the rate was over 100 mm. per hour.

Serum Proteins

Abnormalities of the serum proteins occurred in 10 patients. These consisted principally in a rise of serum globulins, but in 7 cases there was also a decrease in serum albumin.

Urinalysis

Hematuria and albuminuria occurred at one time or other in 11 patients. In 6 of these renal failure developed. These, as well as other cases with renal disease due to vasculitis, will constitute the basis of another report.

Liver-Function Tests

Diminished liver function was noted in 2 patients.

Serologic Tests

No patient had positive reactions in the serologic tests for syphilis (blood Hinton and Kahn) and no patient had a positive L.E.-cell phenomenon (11 patients were tested).

Pathogenesis of "Allergic" Vasculitis

Abell and Schenck,[21] using a technic whereby the blood vessels in a sensitized rabbit's ear could be observed microscopically in vivo, noted the following changes when the rabbit was injected with the sensitizing antigen: arteriolar constriction occurred with stoppage of the circulation; leukocytes adhered to the vascular endothelium and emigrated through the walls of capillaries and venules in large numbers; and some of the leukocytes agglutinated, causing emboli that blocked many capillaries and venules. Rich and Follis[22] demonstrated vascular damage and even rupture of capillaries in sensitized animals when

the specific protein was introduced, but at the same time there was no extravascular cellular injury. Stefanini and Mednicoff[19] reported that, in the serum of patients with anaphylactoid purpura and periarteritis nodosa, an agent (presumably antibody) reacted with an antigen prepared from blood vessels.

"Allergic" vasculitis, then, can occur as the result of a direct antigen-antibody reaction within the vascular wall, which in turn induces a secondary inflammatory reaction in and about the vessel and release of plasma and at times red cells into the tissues. The resulting increase in tissue oncotic pressure is probably responsible for the edema that commonly occurs.

Prognosis

Fifteen of the 30 patients have apparently recovered completely from their episodes of vasculitis. In 12 of these (Cases 1, 2, 5, 10, 11, 12, 13, 15, 16, 17, 18 and 25) the causative factor was recognized and eliminated; in 3 (Cases 14, 22 and 30) spontaneous or steroid-induced recovery has persisted, despite our inability to determine the cause. Seven additional patients (Cases 3, 8, 19, 20, 21, 23 and 26) experienced complete amelioration of symptoms while under treatment with cortisone, but 5 noted a return of symptoms immediately after cortisone was withdrawn and have found maintenance steroid therapy necessary. One patient (Case 3) relapsed three or four weeks after stopping cortisone; another (Case 26) was asymptomatic for eighteen months before relapse occurred. In none of these cases was an allergic factor evident at the onset. Three patients (Cases 7, 24 and 27) have continued to have symptoms, because of irreversible changes produced by the vasculitis; in 2 of these (Cases 7 and 24) remarkable but partial improvement followed steroid therapy. One patient (Case 4) continues to have mild urticaria controlled by antihistamine drugs. Four patients died (Cases 6, 9, 28 and 29); all of them had renal failure.

Treatment

Nineteen of the 30 patients received steroid treatment, several of these on more than one occasion and each time with benefit. It seems that the "allergic" vasculitic reaction is more or less specifically suppressed by adrenal steroids; renal lesions, however, are not regularly benefited by steroid therapy.

Obviously, an important part of the treatment is the elimination of any causative factors present.

Discussion

The clinical pattern of systemic lupus erythematosus has recently been reviewed by Harvey et al.[23] Many of the symptoms and findings of this disease are similar to those encountered in our cases; frequently, allergic reactions herald the onset of lupus and, as previously noted, vasculitis is common in lupus. Thus, it might be argued that some of our patients had variants of the lupus syndrome. Considerable care was exercised in the selection of cases for this study to eliminate all in which such a diagnosis might be justifiable. For example, none of our patients had photosensitivity, a butterfly rash, leukopenia, biologically false-positive serologic reaction or positive L.E.-cell phenomenon. Many of them have been followed for several years, and no clinical course diagnostic of lupus has developed in any.

Periarteritis nodosa is characterized by various combinations of the following: a history of allergic disease; bronchial asthma; neuropathy; nodular visceral and arterial lesions; and eosinophilia and necrotizing involvement of all three coats of medium-sized arteries, with a rich eosinophilic infiltration in and around the vessels. Some of our patients had some of these characteristics, but none had the pathological findings that characterize periarteritis nodosa.

The superficial similarities of some of these cases to lupus erythematosus or periarteritis nodosa might have led to an erroneous diagnosis of either of these disorders in many. We believe that for prognostic reasons it is wise to make the diagnosis of established syndromes only when they seem quite evident.

In the first 18 of our cases the symptoms, signs and clinical courses permitted classification into one of five well recognized clinical syndromes (Table 1). The remaining 12 had for the most part similar symptoms and findings, but in combinations that did not permit classification into known syndromes. It appears that in "allergic" vasculitis any one of a number of physical abnormalities may occur, depending on the degree and location of the vascular involvement. Classification into narrowly defined syndromes is artificial — and embarrassing when new and unexpected signs develop. A more realistic approach would be to indicate that there is "allergic" vasculitis with dermatitis, edema, urticaria, purpura, arthralgia, pneumonitis, nephritis and so on.

The occurrence of edema as a manifestation of "allergic" vasculitis has not previously been emphasized. It must be fairly common and when it occurs as a major complaint in a patient with only minimal additional evidence of vasculitis, the diagnosis of vasculitis may be overlooked. We suggest that skin and muscle biopsies be taken in any patient with peripheral edema of obscure origin. The term "vasculitic edema" may prove useful in the classification of cases similar to Cases 19-21 in our series.

Summary and Conclusions

Vasculitis of varying degrees of severity is commonly encountered in conditions known to be due to hypersensitivity. It is also a common denominator in several conditions of uncertain etiology, but in

which there are strong suggestions that hypersensitivity may be an important factor. It is suggested that the term "allergic" vasculitis be used to designate this disorder.

In a series of 30 living patients with "allergic" vasculitis who did not have systemic lupus erythematosus or periarteritis nodosa, 18 could be classified as having one of five clinical syndromes: contact dermatitis, with generalized sensitization or "id" reaction; urticaria, with angioneurotic edema; vascular purpura; erythema nodosum; or dermatomyositis. The remaining 12 cases could not be classified in any recognizable syndrome.

"Allergic" vasculitis may induce a variety of clinical manifestations, including arthralgias, edema, purpura, fever, weight loss, subcutaneous nodules, pneumonitis, dermatitis, muscle tenderness and weakness, urticaria, neuritis, gastrointestinal bleeding and renal failure.

In some cases peripheral edema without other apparent cause may be induced by "allergic" vasculitis.

Drugs, antibiotics, infective agents and malignant tumors at times function as antigens. Vascular damage probably results from a reaction of antigen and antibody fixed in the vessel wall. Removal of the antigen, if possible, leads to cure.

Cortisone and other adrenal steroids have an almost specific effect on the vascular lesions and promote healing and sclerosis. The prognosis for recovery is good in all cases except those with renal failure.

Case Reports

Contact Dermatitis with Systemic or "Id" Reaction and Vasculitis

Case 1 (N.E.C.H. 92-174). A 63-year-old woman had had stasis ulcers of the legs for many years that had proved resistant to local therapy. Seven days before she was seen she applied an ointment containing neomycin, hydrocortisone and gramicidin, and within a few hours there was a local reaction, characterized by swelling and erythema. In 24 hours a generalized eruption appeared, being most marked on the face and neck. A biopsy was taken from the left upper arm. A vessel deep in the corium showed swelling of all 3 coats, leukocytic infiltration of the vessel walls and perivascular spaces. Other vessels were similarly involved. Conservative dermatologic therapy did not bring about any improvement in 3 days. Consequently, ACTH and, later, cortisone were given, and there was prompt and complete subsidence of the swelling and dermatitis. There has been no recurrence.

Case 2 (N.E.C.H. 92-563). A 58-year-old woman with long-standing rheumatoid arthritis while taking ACTH noticed a rash on the lower abdomen and vulva. ACTH was stopped, and the rash spread to the extremities, chest and back. Dimethisoquin (Quotane) ointment had been used for 5 months to control pruritus vulvae. There was an eosinophil count of 19 per cent. A biopsy of a dermatitic area on the chest showed an inflammatory reaction, with some localization in perivascular areas; capillary endothelium was prominent. The dermatitis subsided partially when the dimethisoquin ointment was discontinued and conservative dermatologic therapy initiated. ACTH therapy was resumed and the dermatitis promptly disappeared.

Urticaria, Angioneurotic Edema and Vasculitis

Case 3 (N.E.C.H. 86-980). A 40-year-old man had recurrent, short episodes of angioneurotic edema of the lips, hands and feet, with occasional scattered urticarial lesions over a period of 2 months. There was moderate dermatographia, but no allergic background. He was found to have heart disease with aortic insufficiency, but there was no past history of rheumatic fever, and the serologic reaction was negative. A biopsy taken from an urticarial lesion on the arm showed marked edema and an inflammatory reaction containing many eosinophils. The process involved the blood vessels. In 3 areas there were collections of blood vessels resembling glomeruli that were involved in the inflammatory reaction. Antihistamine therapy was unsuccessful. He was given short courses of ACTH and later cortisone, each time with immediate relief for several months.

Case 4 (N.E.C.H. 95-516). A 53-year-old woman had had recurrent urticaria and angioneurotic edema for 8 years. No allergies were demonstrable. She obtained no relief from elimination procedures. Biopsy of an urticarial lesion on the arm showed edema and vasculitis in which eosinophils were prominent. Biopsy of an uninvolved area of skin showed healed vasculitis. Treatment was directed toward control of the emotional state. Antihistamine therapy was given symptomatically, and there was moderate improvement. Steroid therapy was withheld.

Anaphylactoid Purpura and Vasculitis

Case 5 (N.E.C.H. 98-737). A 50-year-old man with long-standing rheumatoid arthritis had urticaria on the arms and below the waist, and edema of the face a few days after administration of phenylbutazone. Within 1 week purpura developed in some of the lesions and on the legs. He had taken the drug 5 years before and again 2 months previously, and it caused violent nausea. A biopsy of 1 of the urticarial-purpuric lesions on an arm showed acute vasculitis (Fig. 1). Cortisone in dosage of 100 mg. per day gave only partial relief, but the lesion cleared when the dose of cortisone was increased to 300 mg. a day, and did not return when it was tapered off to 100 mg. daily, the amount necessary to control the symptoms of the arthritis.

Case 6 (N.E.C.H. 43-641). A 63-year-old man manifested a severe reaction 5 days after the 1st and 3 days after the 2d injection of penicillin given for a swollen foot. The reaction was characterized by purpura, fever, muscular pains, peripheral edema and weight loss. Anemia, leukocytosis, albuminuria and signs of uremia ensued. A biopsy of a skin lesion showed an intense necrotizing, exudative vasculitis, with destruction of the vessel and thrombosis. The course was downhill; oral and rectal ulcers developed, and he died in uremia 6 weeks after the initial penicillin injection. At autopsy, lesions similar to those previously seen in the skin were noted in the rectal mucosa, and the kidney showed active glomerulitis (Fig. 6).

Case 7 (N.E.C.H. 73-118). A 59-year-old man underwent a herniorrhaphy. He received a 4-day course of penicillin postoperatively. Sixteen days later pleurisy developed, and a week later joint swellings, myalgia, and purpura began, followed in 2 days by abdominal cramps and diarrhea, which became bloody. There were purpuric spots over the entire body and pneumonia of the right lower lung. The white-cell count was 27,000, and there was marked albuminuria. X-ray study disclosed a large gastric ulcer from which massive bleeding occurred. A moderate degree of uremia developed. Biopsy of the skin showed sclerosing edema of the corium, hemorrhage and infiltration of isolated vessels with polymorphonuclear leukocytes. The symptoms and abnormal laboratory findings gradually subsided with conservative treatment. Two years later the patient was well but still had albuminuria.

Case 8 (N.E.C.H. 75-304). A 43-year-old man began to have episodes of pain, swelling, itching and purpura of the legs. Each episode lasted about 1 week, but was quite debilitating. In 1949 (at the age of 46) he was seen during

1 of these attacks. A biopsy showed an acute, fibrinous, inflammatory reaction around blood vessels. There was only minimal cellular infiltration. This episode subsided spontaneously. During the next 4 years he continued to have similar episodes. On 1 occasion gross hematuria occurred, and cystoscopy demonstrated purpura in the mucosa of the bladder.

He was seen again in 1953 during a moderately severe attack. Biopsy of 1 of the skin lesions showed a much more acute fulminating vasculitis, with an inflammatory exudate. Symptoms subsided promptly with steroid therapy.

CASE 9 (N.E.C.H. 88-470). A 44-year-old man had a nasal discharge, swelling about both ankles, and pain and stiffness of legs and ankles for which he received various drugs. Later, he lost weight, and fever and a purpuric rash developed. The course was intermittent. Eight months after the onset there were no other important clinical and laboratory findings. A biopsy of 2 of the purpuric skin lesions showed focal, acute, necrotizing vasculitis, panniculitis, hemorrhage and swelling and necrosis of collagen. He was treated with full doses of cortisone, with improvement after 3 months. Cortisone was gradually discontinued, and he remained well for 4 months. A purulent nasal discharge and 10 days later, for the 1st time, grossly bloody urine then developed. Gross hematuria continued and cortisone therapy was ineffective. Hypertension and uremia occurred and could not be controlled. He was transferred to another hospital for dialysis on an artificial kidney, which was unsuccessful, and he died. Autopsy showed chronic glomerulonephritis.

CASE 10 (N.E.C.H. 70-900). A 49-year-old man had a resection of the right upper lobe for bullous emphysema and bronchiectasis. The operation was complicated by a bronchopleural fistula, staphylococcal empyema and bacteremia requiring intensive postoperative supportive and antibiotic therapy. He took chloramphenicol in large and later, after discharge from the hospital, in small doses. Two weeks after this therapy had been discontinued, a purpuric eruption appeared over the legs, and low-grade fever developed. He had a normochromic anemia and a rapid sedimentation rate, but the platelet count was normal. Biopsy of a purpuric lesion showed vasculitis, with hemorrhage in surrounding tissues. The rash subsided spontaneously, and he gradually recovered.

CASE 11 (N.E.C.H. 98-787). A 69-year-old man suddenly noticed multiple purpuric lesions on the extremities, some of which were bullous. This occurred 3 weeks after an abdominoperineal resection of the rectum for ulcerative colitis. He had received chloramphenicol orally for a wound infection until 3 days before the purpura began, and was also exposed to potassium permanganate and azochloramid solutions used locally on the operative wounds. Biopsy of a purpuric lesion showed severe acute vasculitis. All therapy was discontinued, and the eruption subsided over a 2-week period.

Anaphylactoid Purpura Combined with Thrombocytopenia

CASE 12 (N.E.C.H. 72-735). A 56-year-old woman began to have attacks of paroxysmal atrial fibrillation, for which she was given quinidine sulfate, with prompt relief. During similar treatment of her 21st attack epistaxis and generalized purpura developed. There was marked thrombocytopenia, for which she received platelet-rich plasma with benefit. A biopsy of 1 of the purpuric lesions showed vasculitis involving capillaries, as well as hemorrhage. She was found to be thyrotoxic and was successfully treated with radioactive iodine.

Erythema Nodosum with Vasculitis

CASE 13 (N.E.C.H. 66-835). A 43-year-old woman had an upper respiratory infection with a sore throat (?streptococcal), for which some tablets were given orally. Two weeks later, while she was asymptomatic, a routine x-ray examination of the chest showed enlargement of the hilar lymph nodes. During the following week red, tender nodules appeared on the legs, together with fever and joint pains. Five years previously enlarged hilar lymph nodes had been noted on x-ray study but had disappeared spontaneously 3 years before the present episode. The tuberculin test was negative. A biopsy of 1 of the nodular lesions showed an acute fulminating vasculitis involving small arterioles and capillaries. Treatment with ACTH followed by cortisone resulted in prompt subsidence of all symptoms. Four weeks later the hilar adenopathy had disappeared.

CASE 14 (N.E.C.H. 70-139). A 20-year-old man had fatigue, weakness, cough, fever, dyspnea and palpitation. A month later a pea-sized nodule appeared over the lower leg. X-ray study of the chest showed round densities throughout both lung fields and hilar adenopathy. He gradually lost 13.6 kg. (30 pounds) in weight. Three months after the onset several nodules appeared on the legs. An axillary lymph node was biopsied and demonstrated only eosinophilia. Biopsy of 1 of the nodules on the legs revealed an active, proliferative, inflammatory reaction centered in the walls and about small blood vessels. An open biopsy of the lung was performed, and there were changes diagnostic of sarcoidosis. He was treated with cortisone for 3 months, and all symptoms subsided. X-ray examination showed gradual and progressive improvement. He has remained well during the ensuing 3 years.

CASE 15 (N.E.C.H. 97-259). A 49-year-old woman had a sore throat. At about the same time she had an infected finger, for which she received an injection of penicillin; 5½ weeks later red, painful, tender nodules appeared on both lower legs, and there was a low-grade fever. X-ray study of the chest showed patchy infiltration of both lower-lung fields and minimal enlargement of the mediastinal and hilar lymph nodes. The sedimentation rate was rapid, and the serum globulin slightly increased. On biopsy of 1 of the nodules a chronic granulomatous panniculitis, proliferation of histiocytes and numerous multinucleated giant cells were seen. Biopsy of a lymph node from the retroscalene area revealed a miliary, granulomatous inflammation consistent with sarcoidosis; some of this material was injected into a guinea pig, but no tuberculosis developed. The patient was treated with cortisone, with prompt subsidence of the lesions on the legs; however, little change occurred in the appearance of the lung lesions over the next month. Six months later she reported that she was well.

Dermatomyositis with Vasculitis

CASE 16 (N.E.C.H. 51-059). A 63-year-old man noted gradually increasing weakness and muscle soreness. About 3 months after the onset, the face and legs became red and edematous, and swallowing became difficult. There was only a slight cough. X-ray examination of the chest revealed a spherical mass in the left upper lobe that proved to be a carcinoma on aspiration of bronchial secretions. A muscle biopsy gave evidence of vasculitis and muscle degeneration (Fig. 5). The diagnoses of bronchogenic carcinoma associated with dermatomyositis were established. Treatment with ACTH was followed by improvement in the edema and muscular weakness. A pneumonectomy for adenocarcinoma, with dissection of metastatic hilar lymph nodes, was successfully carried out. He was maintained on intermittent courses of ACTH for 6 months. There has been no recurrence of either the dermatomyositis or the carcinoma in over 5 years.

CASE 17 (N.E.C.H. 68-029). A 49-year-old woman had a pruritic skin rash on the face, chest and extremities that continued, becoming worse, after dental extractions and administration of phenobarbital or aspirin. After nearly 1 year arthralgias, muscular weakness, peripheral edema and prostration became apparent. X-ray study of the chest showed scarring and questionable cavitation in the upper lobes. A short course of cortisone therapy was given, with improvement in the skin and arthritic symptoms. Cough developed, however, and a few acid-fast bacilli were found in the sputum on 1 occasion, but several sputum cultures were negative and tuberculosis did not develop in guinea pigs after inoculation with sputum. Cortisone was discontinued, and the original symptoms returned. A skin and muscle

biopsy showed mild vasculitis. Cortisone therapy was resumed in full doses, but covered with para-aminosalicylic acid and streptomycin. The patient gradually improved, but treatment was discontinued after 1 month because of the occurrence of allergic reactions to the antimicrobial agents. She has remained well for 2 years.

CASE 18 (N.E.C.H. 55-924). An 18-year-old girl received penicillin for cellulitis of the face. Two weeks later muscle pain and arthralgias occurred and became progressively more severe. Blisters and a scaling dermatitis appeared about the fingernails, and moderately severe peripheral edema was noted. Biopsy of the skin showed edema, perivascular lymphocytic infiltration and vasculitis of small arteries, with thrombosis. On biopsy of muscle similar vascular changes and some necrosis of muscle were seen. She had a moderate anemia, slight eosinophilia, a rapid sedimentation rate, transient albuminuria and slight microscopic hematuria. Treatment with full doses of cortisone caused great improvement, but she did not fully recover until 2 years later. Five years later she was well and had married and borne a baby, but required small maintenance doses of cortisone.

Vasculitic Edema

CASE 19 (N.E.C.H. 95-009). A 53-year-old man had intermittent, nocturnal pain in the distribution of the median nerves of both hands. At the same time puffiness of the hands and moderate pitting edema of the legs below the knees became apparent. Six weeks after the onset numerous studies gave no evidence of cardiac, renal, hepatic or nutritional disease. A biopsy of skin and muscle from the calf area showed an acute vasculitis. Cortisone therapy (100 mg. every 8 hours) was immediately followed by disappearance of the neuritic pains and induction of diuresis, with a weight loss of 6.4 kg. (14 pounds). Steroid therapy was continued, but dosage was gradually reduced to a small maintenance level. Six months after the initial biopsy the patient was well. On another biopsy, taken from a site adjacent to the 1st one, both the skin and muscle gave evidence of healed vasculitis (Fig. 4). Steroid therapy was then withdrawn, but there was a recurrence of neuritis in the hands that could only be controlled with small maintenance doses of steroids.

CASE 20 (N.E.C.H. 98-513). A 50-year-old obese man had marked pitting edema of the feet and legs for 3½ years. Then a bluish discoloration was noted on the backs of the fingers of the right hand, and within a few months both hands became swollen, but not painful. One year later (5 years after the onset) he first came under our observation and was found to have mild diabetes, mild hypertension, hepatomegaly and hypercholesterolemia; extensive studies ruled out cardiac, renal, hepatic and other endocrine diseases. A biopsy from the thenar eminence showed chronic granulomatous inflammatory reactions in the walls of small blood vessels (Fig. 2). Treatment was initiated with a low-calorie diet, prednisone and insulin. He had a moderate diuresis. Three months later another biopsy demonstrated "healing vasculitis" (Fig. 3). His weight had dropped from 99.3 to 79.4 kg. (219 to 175 pounds). Five months after therapy was initiated the edema had practically disappeared, except on 1 hand, where pitting persisted. Attempts to discontinue steroid therapy were unsuccessful, for on each occasion edema reoccurred.

CASE 21 (N.E.C.H. 89-152). A 35-year-old woman had edema of the feet and legs without apparent cause or associated symptoms. Later, puffiness and paresthesias of the hands developed. Extensive laboratory and x-ray studies were negative, except for slight lowering of the serum albumin, which was 2.7 gm. while the globulin was 3.1 gm. per 100 ml., and numerous renal calculi. Biopsies from the leg showed a moderate inflammatory reaction involving small blood vessels in the skin and muscles. Treatment with diuretics was unsuccessful, but soon after initiation of cortisone therapy, diuresis began, and she lost edema fluid amounting to 9.1 kg. (20 pounds) of body weight. Attempts to eliminate cortisone therapy were unsuccessful because of the recurrence of edema and paresthesias whenever dosage was reduced below 75 mg. per day. Repeated biopsies on 2 occasions showed only minimal changes about blood vessels of skin and muscle.

Unclassified Syndromes with Vasculitis

CASE 22 (N.E.C.H. 61-050). A 58-year-old man had a single painful black skin lesion over the left great toe. Over the next 2 years multiple similar lesions occurred on the legs, arms and ears. These gradually increased in size over a period of about 2 months and then they slowly healed, leaving scars. There were no constitutional symptoms. Occasionally, some swelling of the ankles was noted. There was no history of allergy or drug administration. The lesions varied from 2 mm. to 5 cm. in diameter and were purpuric. The feet became so painful that he was unable to walk. Biopsy of a lesion showed an active angiitis involving capillaries and venules; there was a cellular exudate rich in eosinophils and fresh hemorrhage into the corium; some vessels were thrombosed, and there were secondary necrotizing and degenerative changes in the skin. Immediate and dramatic improvement of the skin lesions followed administration of ACTH. When treatment was withdrawn a few petechiae appeared, but these gradually cleared spontaneously and he has had no recurrence for 4 years.

CASE 23 (N.E.C.H. 77-279). A 47-year-old man with a past history of asthma had spontaneous ascites 3 months after a transurethral prostatic resection. Fever, weight loss, aching and tenderness of the feet and hands and a petechial rash in exposed areas then developed. He was found to have hepatomegaly, muscle tenderness and sensory loss on all extremities. There was no leukocytosis, but an eosinophilia (count of 42 per cent) was present. The albumin-globulin ratio was reversed. Biopsy of the skin showed an acute inflammatory reaction in the capillaries, with hemorrhage; on muscle biopsy degeneration and segmentation of sarcoplasm were seen. Cortisone treatment resulted in marked improvement but maintenance steroid therapy has been necessary (75 mg. of cortisone a day) for over 2 years.

CASE 24 (N.E.C.H. 94-509). A 54-year-old man had a productive cough. Six weeks later several muscle groups became quite painful, and fever and weight loss became apparent. Laboratory study showed a rapid sedimentation rate, a reversed albumin-globulin ratio and markedly deranged liver function. X-ray study of the chest disclosed diffuse interstitial pneumonitis, with small nodular areas. A purpuric rash developed. The fever (maximum temperature of 103°F.) promptly subsided when iodide therapy was discontinued. A muscle biopsy revealed necrotizing arteritis involving all 3 coats of the arteries. Cortisone therapy was initiated, with gradual, progressive, but only partial improvement.

CASE 25 (N.E.C.H. 65-346). A 56-year-old woman had pain and stiffness in various muscles and about joints and mild fever over a 2-month period. Subcutaneous nodules appeared on the forearms after she took anacin. Biopsy of 1 of these nodules showed an active inflammatory reaction involving medium-sized blood vessels, and on muscle biopsy Zenker's degeneration was evident. ACTH and later cortisone therapy over a 9-month period resulted in relief of symptoms. Shortly after this therapy was stopped, evidence of a partial occlusion of the right axillary artery appeared. Cortisone was resumed for 2 months, and all symptoms subsided. One year after cortisone was discontinued there was no evidence of the vasculitis, but the patient had hypertension, which had previously not been present.

CASE 26 (N.E.C.H. 52-431). A 22-year-old man noticed tender lumps in the skin of the posterior thorax. These persisted, and later cervical and axillary lymphadenopathy was noted. Four months later he had pain in 1 wrist, and a purplish nodule appeared on 1 forearm. In another month a low-grade fever and pain in the leg muscles developed. He lost 13.6 kg. (30 pounds) in weight. There was a moderate anemia. A skin biopsy showed vasculitis involving medium-sized and small arteries and veins. Fever and pain subsided, and the nodules disap-

peared, when ACTH in small doses was given, but weakness and stiffness of the muscles persisted and he was unable to walk. The nodules recurred when treatment was discontinued. A muscle biopsy demonstrated an intense vasculitis involving arteries and veins, and there was interstitial serous inflammation and some necrosis of muscle. Intensive therapy with ACTH resulted in a marked improvement. After 4 months of therapy he was considered well, and steroid therapy was discontinued. After 18 months of good health there were recurrences of joint pains, subcutaneous nodules and induration of muscles. A muscle biopsy 2½ years after the 1st biopsy again showed necrotizing vasculitis centered in small arterioles. The symptoms again responded to ACTH.

CASE 27 (N.E.C.H. 101-110). A 64-year-old man had had a productive cough and dyspnea since an automobile accident 6 years previously. During the same time he had recurring, painful, red-purple skin lesions on the arms and legs for a few days. During a 1-year period there was pain and swelling of the proximal interphalangeal joints. Laboratory studies showed marked anemia, eosinophilia (count of 20 per cent), albuminuria and microscopic hematuria, nitrogen retention, hyperglobulinemia and a greatly elevated sedimentation rate. X-ray examination of the chest showed bullous emphysema and saccular bronchiectasis. On biopsy of a purpuric skin lesion marked vasculitis was seen. Renal biopsy gave evidence of chronic pyelonephritis or glomerulonephritis. Steroid therapy with withheld because of uremia and infection.

CASE 28 (N.E.C.H. 13-847). A 39-year-old man with a past history of tuberculosis and hypertension had headache, fatigue, epigastric distress and diarrhea, for which he received symptomatic treatment (? sulfonamides). Two weeks later migratory arthralgias began. Later, he had pleuritic pains and low-grade fever, and was found to have a heart murmur, lymphadenopathy, albuminuria, splenomegaly and renal failure. Biopsy of a lymph node showed only reactive hyperplasia. On a muscle biopsy vasculitis of arterioles was apparent. The course was downhill. Petechial hemorrhages appeared, and he died of uremia 6 months after the onset of symptoms. Autopsy disclosed small hemorrhages throughout the kidneys, with engorged and sclerotic glomeruli, some of which showed "wire-loop" lesions.

CASE 29 (N.E.C.H. 28-400). A 60-year-old woman first had a sore throat and then laryngitis, migratory arthralgias and erythematous nodules, which appeared and disappeared. These symptoms continued with variable severity for 4 years. Cough, with hemoptysis, sores in the mouth, edema, weight loss, abdominal tenderness and episodes of vomiting ensued. She was anemic, with albuminuria and evidence of renal failure. Biopsy of 1 of the subcutaneous nodules showed a violent necrotizing vasculitis involving arterioles. The clinical course was gradually downhill, and she died in uremia about 2 years later.

CASE 30 (N.E.C.H. 29-802). A 46-year-old man gave a history of attacks of urticaria and arthralgias, each lasting approximately 10 weeks and occurring annually each fall for 13 years. The 1st attack was associated with diarrhea, muscle pain, fever, pneumonitis and eosinophilia. A few months before examination he vomited blood and was found to have a duodenal ulcer. He gave a history of seasonal allergic rhinitis in the spring and summer. He was examined during an episode of urticaria and arthritis and found to have fever, anemia, eosinophilia (count of 57 per cent), impaired liver function and a pleural effusion. A muscle biopsy showed a moderate vasculitis involving small arterioles. There was no microscopical or immunologic evidence of trichinosis. He was given aspirin and Pyribenzamine. The symptoms gradually subsided over a 4-month period. Seven years later (at the age of 53) he reported that urticaria and joint symptoms recurred from time to time, but that he was not incapacitated and was able to work every day.

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Correction. On the cover and first page of the July 5 issue of the *Journal* the third author's name in the article, "Rupture of the Heart after Myocardial Infarction," should be Gustave A. Laurenzi, M.D., instead of Gustave A. Laurenz, M.D.

EASTERN EQUINE ENCEPHALOMYELITIS IN MASSACHUSETTS IN 1955*

Report of Two Cases in Infants

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THE virus of eastern equine encephalomyelitis, on invasion of the human central nervous system, can result in an acute febrile illness, with rapid development of coma and convulsions, that is frequently fatal, occasionally allows survival with permanent brain damage, or less often subsides, with complete recovery.

FIGURE 1. *Section of the Pons in Case 1, Showing Perivascular Cuffing, with Neutrophilic and Mononuclear Cells (Hematoxylin and Eosin Stain X250).*

This agent was first demonstrated to be pathogenic for man in the course of an epidemic of 38 cases in eastern Massachusetts in the late summer and autumn of 1938.[1-3] During the next ten years small groups of cases were recognized in coastal regions of Texas and Louisiana,[4-6] and in 1948-49 a circumscribed epidemic of 13 cases occurred in the Dominican Republic.[7]

The purpose of this paper is to report 2 cases occurring in infants in eastern Massachusetts during the poliomyelitis epidemic of 1955, to review the current and interim occurrence of this disease in human and nonhuman hosts and to consider the present knowledge of the epidemiology of the disease.

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CASE REPORTS

CASE 1. S.R.S. (C.M.C. A-435215), a 7-month-old boy, was admitted to the Children's Medical Center on October 20, 1955, with a tentative diagnosis of poliomyelitis. Six days previously the parents and a 4-year-old sibling had had mild afebrile diarrhea lasting for 2 or 3 days. Two days before entry fever developed (with a maximum temperature of 101°F.), suddenly rising to 104°F. during the night before entry; at that time examination was negative except for the fever. Re-examination on the day of entry showed a temperature of 104°F., a slightly stiff neck, drowsiness and no localizing neurologic signs. The white-cell count was 18,000; the spinal fluid had a normal sugar content and contained 30 white cells per cubic millimeter, with 40 per cent neutrophils, no bacteria on smear or culture and a total protein of 15.6 mg. per 100 ml. Within 6 hours the spinal-fluid count had risen to 1550, with 94 per cent neutrophils and normal sugar; the temperature was 105°F., and the patient was comatose. Because of the possibility of meningitis, antibiotic and intravenous fluid therapy was begun.

Seventeen hours after admission, after a gradual fall in temperature to 101°F., a symmetrical generalized tonic-clonic convulsion began that could be controlled only with extensive use of paraldehyde and ether; the clonic nature of the seizure gradually assumed a fine, fluttering character and then ceased 26 hours after entry. The peripheral white-cell count was now 45,000, with a marked shift to the left; the spinal fluid contained 2100 cells per cubic millimeter, with 60 per cent neutrophils and a total protein of 65 mg. per 100 ml.

The patient continued to be comatose, but his condition was stable, with a temperature of 101°F.; reflexes were absent; the right pupil became dilated, but the optic fundi remained normal; edema developed in the eyelids, scrotum and legs. Forty-eight hours after entry respirations ceased; an endotracheal tube was inserted and he was satisfactorily maintained in a respirator for 6 hours, after which circulation failed and he died. All spinal-fluid cultures had remained negative.

Post-mortem findings of significance were limited to the brain, which weighed 1080 gm. (normal, 691 gm.). When the skull was opened the cerebrum oozed out under pressure; the convolutions were flattened, and the consistence soft; vessels were congested; a pressure cone was present. There were no petechiae or exudate; the ventricles were not dilated.

Microscopical examination showed perivascular cuffing, with lymphocytes and neutrophils as well as some diffuse cellular infiltration (Fig. 1 and 2). There was no hemorrhage. The neurons were shrunken and surrounded by phagocytic cells. No inclusion bodies were seen. These changes were most marked in the pons and hippocampus, less pronounced in the cerebrum and spinal cord, and absent in the medulla and cerebellum.

Sections of the brain were homogenized in phosphate buffer and inoculated intracerebrally into 20-gm. mice (Carworth Farms, Webster strain). An agent causing death with ataxia and stupor in 3 or 4 days was carried through 5 mouse passages, with an $L.D._{50}$ of approximately 4×10^{-12} ml. of infected mouse brain. Hippocampal lesions were striking (Fig. 3). The agent was identified as the virus of eastern equine encephalomyelitis by the United States

Public Health Service Communicable Disease Center, Montgomery, Alabama, with the mouse neutralization test.

CASE 2. T. D. (B.F.H. 24925),* an 11-month-old boy from South Weymouth, Massachusetts, entered the Boston Floating Hospital on September 14, 1955, in coma. Three days before entry the temperature rose rapidly to 105°F., with the onset of a left-sided clonic convulsion; there was a brief period of diarrhea. Progressively increasing drowsiness developed, with intermittent convulsions only partially controlled by phenobarbital; the temperature subsided, and respiration was well maintained. The patient was hospitalized because of failure to feed.

On physical examination he responded only to painful stimuli, and had a flat fontanelle and constricted, nonreactive pupils; the extremities were limp, but deep tendon reflexes were present and symmetrical; plantar stimulation gave dorsiflexion; the neck resisted flexion.

The temperature was 99.4°F., the pulse 122, and the respiration 24.

Lumbar puncture showed 326 cells, largely lymphocytes, per cubic millimeter. The sugar was diminished (negative 5-tube test), but smear and culture were negative. The white-cell count was 19,400, with 82 per cent neutrophils. Subdural taps were negative.

Because of an initial suspicion of meningitis, antibiotic therapy was instituted but was without effect. Convulsions continued for 48 hours despite the use of phenobarbital and

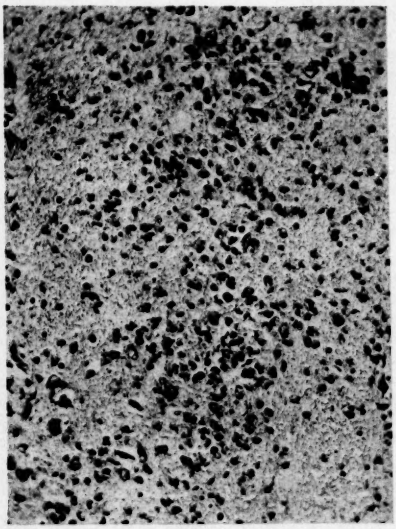

FIGURE 2. *Section of the Pons in Case 1, Showing Neuronolysis and Diffuse Infiltration with Neutrophilic and Mononuclear Cells (Hematoxylin and Eosin Stain X250).*

Dilantin. The fever did not recur. An electroencephalogram showed no abnormality. The patient was digitalized because of a rising pulse and respiratory rate and increasing heart size, and responded well.

Consciousness was never regained, the patient remaining completely vegetative, but adequate nutrition was maintained by gavage feeding. He was discharged on November 4. Six months after the onset of the illness his condition remained unchanged.

*Included with the permission of Dr. James M. Baty.

Acute-phase and convalescent-phase serum samples examined at the United States Public Health Service Communicable Disease Center, Montgomery, Alabama, showed a rise in complement-fixation titer diagnostic of eastern equine encephalomyelitis.

The marked rise in spinal-fluid and peripheral white-cell counts expected in this disease was not

FIGURE 3. *Section of the Hippocampus of a Mouse Infected with Virus from Case 1, Showing Progressive Destruction of the Pyramidal Cells of the Stratum Lucidum (Hematoxylin and Eosin Stain X30).*

The animal was killed, and the brain fixed at once to avoid post-mortem changes, to which this area is very susceptible.

observed here, presumably because the most acute stage of the disease had passed before entry to the hospital. The low spinal-fluid sugar on admission may be attributable to three days of inanition during severe illness. Contrary to the situation with meningitis, one cannot believe that earlier hospitalization would have altered the ultimate outcome.

Neither patient had had any unusual exposure to mosquitoes.

DISCUSSION

The clinical features of both these cases and the pathological findings in Case 1 are entirely consistent with those reported by Farber et al.[3] It should be noted, however, that neither the clinical nor the pathological picture is specific for this type of encephalitis. St. Louis, western equine and herpes-simplex encephalitis exhibit many of the same features. However, elevation of the peripheral and

spinal-fluid white-cell counts, and predilection for hippocampal lesions are particularly pronounced with the virus of eastern equine encephalomyelitis.

In 1938, when human cases were first recognized, there was a circumscribed epidemic in southeastern Massachusetts, west of Cape Cod (Norfolk, Plymouth, and Bristol Counties). Between June 4 and October 15, 248 horses died of encephalitis, with 68 cases occurring during the week of August 27. During the same period there were at least 38 proved or probable cases in human beings, with a peak incidence in the week of September 3.[1]

Because of the interest stimulated by this epidemic, encephalitis in human patients was made reportable, but the Massachusetts Department of Public Health records no further cases until the reappearance here reported. A scattering of cases in horses and mules has continued to appear; Table 1 shows the occurrence in these hosts over the past eighteen years. Attack rates cannot be estimated because of lack of accurate figures on annual equine population.* In addition, an infected catbird (*Dumetella carolinensis*) was shot in Bridgewater in 1953, in the same county where two horses died in that year.[8]

In 1955, between August 18 and October 4, 44 horses died of eastern equine encephalomyelitis in Bristol, Norfolk, Plymouth, Middlesex and Worcester counties, with a peak incidence during the week of August 28. In addition, the disease was identified in domesticated pheasants in Swansea, Mattapoisett, Millis and Norfolk. Four proved cases appeared in human beings, from South Weymouth (September 14, as mentioned above), Brighton (September 25), Hingham (September 26) and Norwood (October 19, as mentioned above).[8] The geographic distribution is shown in Figure 4.

The 1955 summer season had been exceptionally rainy, with 17.09 inches of rain in August. The situation had been similar in 1938, with 15.76 inches in June and July after a wet spring. The only other moderately wet season between these years was 1946, with 9.92 inches in August after several abnormally dry months. The normal mean monthly rainfall in this area at any season is 3 to 3.5 inches.[9]

Elsewhere, the disease has been reported infrequently. Coastal Texas experienced a few cases in 1941 and thereafter, and there were at least 10 human cases in Louisiana in 1947.[4-6] There were 20 recorded avian outbreaks on New Jersey pheasant farms in the years 1947-1951.[10] In 1954 there were 4 proved or probable equine cases in Wisconsin, but human beings were not known to be affected.[11] Recovery of the virus from chicken mites and lice in Tennessee was reported in 1948.[12] A carefully studied epidemic in the Dominican Republic in 1948-49 included 13 human and 516 equine cases in a three-month period.[7] Hence, it is clear that the virus is widely distributed, but conditions leading to dissemination to man appear to occur infrequently.

Recently, quantitative data on the spread of the virus have been reported.[13-19] Although it has been evident for some years that mosquitoes can transmit the disease experimentally, these studies have demonstrated, first, that the virus multiplies in susceptible mosquitoes so that the insect, after a two-week intrinsic incubation period, remains infective for a month or two; secondly, different mosquito species vary in the host-blood virus titer necessary to infect them, and, finally, although the dose of virus inoculated by an infected mosquito varies greatly, some individual mosquitoes have been demonstrated to have inoculated a dose fatal to a horse. Studies of antibodies in wild birds in an endemic swamp area in Louisiana showed that large wading birds (such as egrets and ibises) have a high incidence of neutralizing antibodies whereas small songbirds, such as the redwing blackbird (*Agelaius phoeniceus*), lack antibodies. When experimental infections were undertaken, the wading birds showed low mortality, but a "subinfective" virus titer whereas the redwings and other small songbirds had high virus titers but died

TABLE 1. *Eastern Equine Encephalomyelitis in Horses and Mules in Massachusetts, 1938-1955.**

YEAR	NO. OF CASES	FATALITY RATE
		%
1935	0	—
1936	0	—
1937	0	—
1938	297	93.2
1939	15	73.3
1940	8	50.0
1941	0	—
1942	6	33.0†
1943	2	100.0
1944	2	50.0
1945	0	—
1946	4	75.0
1947	1	100.0
1948	2	100.0
1949	1	100.0
1950	1	100.0
1951	0	—
1952	1	100.0
1953	2	100.0
1954	0	—
1955	44	100.0

*Based on annual reports of U. S. Dept. of Agriculture, Bureau of Animal Industry, Washington, D. C.

†Some of these cases occurred in March & diagnosis therefore suspect.

*There is disagreement between the figures for annual equine populations as available from the United States Department of Agriculture, Bureau of Animal Industry, and from the Commonwealth of Massachusetts, Department of Agriculture, Livestock Disease Control Section. The number has probably varied between 10,000 and 20,000.

within 24 to 48 hours. An intermediate but probably highly significant position was occupied by the grackle (*Quiscalus quiscula*), which maintained a titer far above the mosquito infective level for many days but failed to succumb. The horse (and perhaps by analogy the human being) was considered to be merely a "dead-end" or "indicator" species in the natural epidemiologic chain: the maximum viremia in experimentally infected horses barely reached the infective level for the most susceptible mosquito species. Pursuit of studies such as these will undoubtedly clarify the epidemiologic problem.

Certain evidence suggests, however, that the mosquito is of importance only in certain seasons and in certain situations. The occurrence of cases in human patients and horses has regularly ceased with the advent of dry or cold weather — in other words, factors limiting the mosquito population. But on pheasant farms it has been noted that an epizootic may be severe in one pen but spare adjacent pens, and one such outbreak in Chester, New Jersey, continued until December 5, well after frost.[10] Such observations suggest transmission by an ectoparasite rather than the mosquito. The presence of the virus of eastern equine encephalomyelitis in chicken mites and lice has been proved[12]; demonstration of ability of these arthropods to maintain this virus through a period of dormancy and subsequently to transmit it to susceptible hosts would go far to explain the "wintering-over" problem and the seasonal incidence of the recognized disease, but Chamberlain and Sikes[20] have found bird mites to be very inefficient vectors of the virus for baby chicks in the laboratory.

Experimental data[14,18,19] indicate that variations in severity of the disease in different individuals of a species may be at least in part a function of dose of inoculum. It is possible with a sufficiently small inoculum in the horse to cause development of neutralizing antibodies without detectable viremia or clinical symptoms. A larger dose also results in viremia, and with a still greater inoculum, viremia is associated with a transient febrile episode. Finally, a sufficiently large inoculum produces, in addition to prodromal symptoms and viremia, a subsequent full-blown clinical encephalitis leading to death or occasionally to recovery with or without sequelae. The initial development of neutralizing antibodies coincides with subsidence of the viremia and precedes slightly the onset of clinical evidence of central-nervous-system disease.

These considerations suggest that there should be evidence of mild or subclinical disease in human beings. Two cases in adults in Massachusetts in 1955 (Brighton and Hingham), with complete recovery after mild encephalomyelitis, are reported currently by Webster in the succeeding article in this issue of the *Journal*. Only 1 of the 1938 Massachusetts cases ended in complete recovery.[21]

Studies in the Dominican Republic epidemic showed neutralizing antibodies against eastern equine encephalomyelitis in 17 per cent of asymptomatic persons over eleven years of age in the epidemic area (children under eleven were vaccinated during the outbreak) but none in the surrounding dry areas.[7] In Louisiana, in 1947, 2 household contacts of patients had neutralizing antibodies without a history of disease.[6] But in a study of the Louisiana region where the wild-bird studies mentioned above were performed in an area where the disease is enzootic

FIGURE 4. *Map of the Counties of Eastern Massachusetts, Showing the Distribution of Eastern Equine Encephalomyelitis in Various Hosts in 1955.*

in horses and presumably in birds, only 4 of 51 men who had spent over ten years lumbering in the swamp had neutralizing antibodies. All of 18 nearby farmers lacked antibodies.[16]

The conditions necessary for the appearance of eastern equine encephalomyelitis in man are not entirely clear. An abundance of mosquitoes is a prerequisite, and this is in turn favored by an abnormally wet period followed by a warm dry spell. These conditions were present in the two Massachusetts outbreaks, but apparently no abnormal precipitation preceded the Louisiana outbreak, and that in the Dominican Republic was stated to be in a season of normal rainfall. The accumulation of susceptible persons is of no importance, since immunity appears to be the exception. The frequency of disease in horses is likewise unimportant, except as an indication of the presence of disease, if the horse is truly unable to infect the mosquito. And since the vector

species of arthropods and the wild-host species of birds are at the moment not definitely known, the existence of or the circumstances favorable for a wild epizootic are not likely to be recognized. However, it is reasonable to assume that a wild epizootic must precede overflow to horses and to man and that the presence of an enlarged mosquito population must favor both epizootic and overflow. Bird ectoparasites seem unimportant in human disease; although bird mites may attack human beings, no direct or circumstantial evidence of such transmission has been reported.

No efforts were made to ascertain the probable mosquito vector in Massachusetts in 1955. In a mosquito study in 1939,[22] *Aedes vexans* was implicated on the basis of frequency and widespread distribution, *A. triseriatus* being found to be only 7 to 20 per cent as common in most areas, and *A. sollicitans* ranging a maximum of 15 miles away from salt water. However, Chamberlain et al.[16] have recently shown that *A. sollicitans* and *A. triseriatus* have a vector efficiency for eastern equine encephalomyelitis about four times as great as that of *A. vexans,* so that no specific assumption can be made. Only 3 of the 1955 cases in horses and 2 outbreaks on the pheasant farms occurred more than 15 miles from salt-water estuaries.

Control of the disease in human beings, therefore, seems to rest largely on general regional methods of mosquito control, with increased attention to abnormally wet seasons. Active immunization with inactivated chick-embryo-grown virus is feasible[23] and presumably reduced the number of cases in the Dominican Republic outbreak.[7] Immunization ordinarily is used only on a small scale, however, either after recognition of the presence of an epidemic or for the protection of laboratory workers. The immunity requires frequent renewal and is unlikely to become a general procedure. Horses may be similarly protected, but for reasons stated above this would presumably fail to affect human incidence.

It is probable that the disease in human patients is not always recognized, and it is particularly possible that in 1955 mild cases were mistaken for an encephalitic form of poliomyelitis. Proper laboratory procedures are essential to confirm the diagnosis: a seventeen-month-old baby was seen at this hospital in September, 1955, with an illness that was clinically and pathologically consistent with eastern equine encephalomyelitis, but the virus of herpes simplex was the only agent isolated. It is therefore imperative to obtain acute-phase and convalescent-phase serum for neutralization and complement-fixation tests, or postmortem brain for animal inoculation.* Virus isolation from the brain becomes difficult within four or five days after the onset of encephalitis, but neutralizing antibodies rise rapidly after this period.

*Fresh-frozen material, whole or homogenized in phosphate buffer in a 20 per cent suspension, should be stored at −70°C., and instructions for further handling sought from the State Laboratory.

Summary and Conclusions

Two cases of eastern equine encephalomyelitis in infants, 1 fatal and 1 leading to severe, permanent brain damage, occurring in eastern Massachusetts in the autumn of 1955, are reported. In addition there were in the same outbreak 2 cases in adults, without sequelae, 44 fatal cases in horses and 4 extensive outbreaks in pheasant farms.

The experience in this area since the first human outbreak in 1938 is reviewed, and the present knowledge of the epidemiology of the disease is considered.

It is probable that the virus is enzootic in wild birds, in which mites and lice, as well as mosquitoes, may play a part in transmission, and that conditions favorable for increase in mosquito populations are associated with overflow into equine and human populations. The fact that the virus titer developed in the horse is not infective for the mosquito suggests that this quadruped is merely an "indicator" species rather than a link in the epidemiologic chain. Control of the disease in human beings may be accomplished by mosquito-control measures and in certain situations by active immunization.

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EASTERN EQUINE ENCEPHALOMYELITIS IN MASSACHUSETTS*

Report of Two Cases, Diagnosed Serologically, with Complete Clinical Recovery

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VIRAL diseases of the nervous system, except mumps, poliomyelitis and herpes zoster, are extraordinarily rare in New England. Although patients on the wards of general hospitals are frequently suspected of having viral meningitis or encephalitis, such diagnoses are seldom confirmed by appropriate laboratory tests or post-mortem examination.

During the summer of 1955, at the peak of the poliomyelitis epidemic, 2 cases with a clinical picture consistent with a viral meningoencephalitis were observed on the Neurology Service of the Massachusetts General Hospital. They differed from the usual cases of poliomyelitis and were suspected of being some other type of neurotropic viral infection. Antibody determinations on serum obtained during the acute and convalescent phases of the illness led to the disclosure that, in both cases, the disease was due to the virus of eastern equine encephalomyelitis. Since these were the first cases known to have occurred in this geographic area since 1938, and since the clinical picture deviated from that seen previously, it was thought advisable to call them to the attention of the medical profession and to review, briefly, some of the important characteristics of this disease.

In the United States, encephalitis in horses was first shown to be due to a virus immunologically distinct from that of Borna disease by the studies of Meyer et al.[1] that followed the 1930 epidemic in California's San Joaquin Valley. In an address to the American College of Physicians in 1932 Meyer[2] outlined the essential clinical and pathological features of the equine disease and mentioned that 3 cases of encephalitis in human beings had been reported, in 1 of which post-mortem examination showed lesions in the brain similar to those described in horses. In 1933 a second filtrable virus was isolated from diseased horses in an epidemic in Virginia, Delaware, New Jersey and Maryland, thus establishing the existence of eastern and western types of equine encephalomyelitis.[3] By 1934 workers in two laboratories had demonstrated that several species of mosquitoes could serve as a possible vector for the viruses of both types.[4,5] The relation between the human and equine forms of the disease was further defined by a brief report of 6 human cases of encephalitis during August and September, 1937, in Northern Minnesota.[6] All the patients were farmers, and 5 had had contact with sick horses. Two died after an acute illness of four or five days' duration, and post-mortem examination in 1 showed severe degeneration of nerve cells in the cervical cord, with nests of lymphocytes, a mild lymphocytic reaction in the meninges and perivascular cuffing throughout medulla, midbrain and cerebral cortex. A rise in neutralizing antibody titer for the western form of the disease was demonstrated in 1 of the patients who recovered.

In the following year 34 human cases of eastern equine encephalomyelitis occurred in Massachusetts, with a 74 per cent mortality. In 9 patients, virus was isolated from the brain, and 8 others had characteristic brain lesions at port-mortem study. Ten had a significant rise in neutralizing antibodies, and 7 other fatal cases without autopsy were thought to be consistent with the characteristic clinical picture. The clinical features, pathology and technic of virus isolation were outlined in numerous reports.[7-11] Subsequently, the clinical status of the survivors was described after one[12] and nine years.[13] From 1938 to 1955, no human cases were reported in Massachusetts, and a review of the literature yields only 18 others from all parts of the United States.[14-17]

CASE REPORTS

CASE 1. M.G.H. (906894), a 40-year-old male shipping clerk residing in Hingham, Massachusetts, was admitted to the Neurology Service on September 26, 1955. Nine days previously he had noted rhinorrhea, malaise and an unusual, severe aching in his muscles. He remained at home for 4 days and then felt well enough to return to work. Late in the afternoon of the day before admission, he first noted a steady, bifrontal headache that gradually increased in severity. On retiring, he was unable to sleep and had several brief episodes during which his arms and legs "shivered."

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These were unaccompanied by a change in state of consciousness, feverishness or chattering of teeth. At midnight, he got up and, while preparing coffee, had another "shivering spell." The temperature was 101°F. A few minutes later he had a generalized tonic-clonic seizure lasting 1 minute. He was given 600,000 units of procaine penicillin and Demerol by a physician and remained unresponsive for the next 11 hours; he then had another generalized seizure. Four hours later, on the Emergency Ward, he had 2 more tonic-clonic convulsions beginning with head turning to the right. No other member of the family had had a similar illness. Early in September a distant neighbor's horse had been sacrificed after a clinical diagnosis of encephalitis had been made by a veterinarian. With this exception there were no sick horses, pets or other farm animals in the neighborhood. The past and family histories were noncontributory.

Physical examination showed a well developed and well nourished man. He was comatose, his only response being withdrawal of the limbs from painful stimuli. He had a small laceration of the lip and mild nuchal rigidity. The remainder of the general examination was normal. No abnormalities of the cranial nerves were found. Movements of the limbs evoked by painful stimuli were co-ordinate. There was no abnormality of posture or tone. The tendon reflexes were equal and active, as were the abdominal and cremasteric reflexes; the plantar reflexes were flexor.

The temperature was 99.4°F., the pulse 96 (with normal sinus rhythm) and the respirations 20. The blood pressure was 115/80.

Examination of the blood showed a hemoglobin of 14.8 gm. per 100 ml. and a white-cell count of 11,900. The blood Hinton test was negative. The cerebrospinal fluid was under a pressure equivalent to 160 mm. of water and contained 100 white cells per cubic millimeter, of which 50 per cent were neutrophils and 50 per cent lymphocytes, with a total protein of 63 mg. and a sugar of 97 mg. per 100 ml. The spinal-fluid Hinton test was negative as was heterophil-antibody agglutination, and 2 blood cultures showed no growth.

The seizures were controlled by Dilantin and phenobarbital; fluid and electrolyte balance were maintained by intravenous infusions. On the following day, he was still comatose. Both eyes deviated slightly to the right, and there was a mild right-sided hemiparesis affecting the face, arm and leg. The biceps, radial and ankle reflexes were absent bilaterally, and both plantar reflexes were still flexor. The white-cell count was 20,500, with 75 per cent neutrophils, 17 per cent lymphocytes and 8 per cent monocytes. An electroencephalogram was abnormal, showing random, asynchronous, diffuse, slow activity bilaterally that was prominent in the frontal regions. A 2d lumbar puncture revealed a cerebrospinal fluid under a pressure equivalent to 320 mm. of water, containing 141 white cells per cubic millimeter, with 60 per cent lymphocytes and 40 per cent neutrophils and a total protein of 156 mg. and a sugar of 113 mg. per 100 ml. X-ray films of the chest and skull were normal.

No further seizures occurred, but the patient remained critically ill until the 5th hospital day, when he became more responsive. On the following day he took fluids by mouth and spoke for the 1st time. Six days after admission he was alert and oriented, and within 2 more days, he was walking around the ward. On October 7, 3 days before discharge, a 3d lumbar puncture was performed: the cerebrospinal-fluid pressure was equivalent to 215 mm. of water, and the fluid contained 29 white cells per cubic millimeter; the total protein was 49 mg. and the sugar 80 mg. per 100 ml. A 2d electroencephalogram revealed 3-per-second slow waves that were more prominent over the left cerebral hemisphere. The patient was next seen in the Outpatient Department on October 31, when detailed physical and neurologic examinations were negative. Lumbar puncture revealed normal cerebrospinal-fluid pressure containing 3 lymphocytes per cubic millimeter, with a total protein of 36 mg. per 100 ml. The electroencephalogram showed a return toward normal, with only occasional slow waves frontally. He returned to work and, 3 months later, was asymptomatic.

CASE 2. (M.G.H. 906861), a 48-year-old housewife living in Brighton, was admitted to the Neurology Service on September 25, 1955. Ten days previously, she had a temperature of 102°F., which subsided after 6 hours. On the following day, she did her housework and was able to help out in the family store during the evening. No further symptoms occurred until 5 days before admission, when, after a quick lunch and while she was hurrying from the house, her "mind went blank" for several moments. No faintness, weakness, vertigo, headache or change in visual, sensory and motor function were noted. She did not feel better during the rest of the day but carried on with her usual activities. On the next day she had a poor appetite, and felt slightly dizzy and nauseated. Generalized, steady headache appeared during the evening. Three days before admission, her headache was worse and on sitting up, she had definite vertigo, diplopia with horizontal displacement of images and an unsteadiness of gait that was so marked that she had to be assisted when walking. She felt slightly feverish and noted that sudden changes in head position increased her dizziness. A physician, who saw her later in the day, found her temperature normal, and prescribed Dramamine. By evening, she was slightly confused, and her headache was worse. During the remaining interval before admission, she was confused and was later unaware of what had happened. Her family remarked that her headache, dizziness and confusion had become worse. She was drowsy and unable to eat or drink because of nausea. She vomited several times daily and was too ataxic to walk.

She had not been exposed to sick animals or to another person with an infectious illness. The family and past histories were noncontributory.

Physical examination showed a somnolent and slightly confused woman. She was oriented, could answer simple questions briefly and could follow commands but was unable to carry on a conversation. Her attention span was brief and her affect was described as "flat." There was a slight asymmetry of the face but no definite weakness; the remaining cranial nerves were normal. The neck was moderately stiff on forward bending. There were no abnormalities of motor power, tone, co-ordination or sensation. The tendon reflexes were graded as +++; the abdominal reflexes were absent, and the plantar reflexes were flexor.

The temperature was 99.2°F., the pulse 100 and regular, and the respirations 12. The blood pressure was 105/60.

Examination of the blood disclosed a hemoglobin of 13 gm. per 100 ml. and a white-cell count of 26,000, with 91 per cent neutrophils, 5 per cent lymphocytes and 4 per cent monocytes. The urine was normal except for a ++ test for albumin and 10-20 white cells per high-power field in the sediment. Lumbar puncture showed a cerebrospinal-fluid pressure equivalent to 120 mm. of water, with 415 white cells per cubic millimeter, 85 per cent of which were lymphocytes and 15 per cent neutrophils. The total protein was 107 mg., and the sugar 71 mg. per 100 ml. The blood Hinton test and heterophil-antibody agglutination were negative.

The patient received fluids parenterally and improved steadily from the time of admission. On the following day, x-ray films of the chest and skull were normal. An electroencephalogram was markedly abnormal, showing random, diffuse slow waves over both cerebral hemispheres. Five days after admission, she was ambulatory and asymptomatic, and on October 3, the day before discharge, the white-cell count was 9500. A 2d lumbar puncture revealed clear cerebrospinal fluid under a pressure equivalent to 105 mm. of water, with 45 lymphocytes and a total protein of 59 mg. per 100 ml. She was seen at monthly intervals, and thereafter remained asymptomatic, exhibiting no neurologic abnormalities.

Three serum samples from each patient were forwarded through the Massachusetts Department of Public Health to the Communicable Disease Center, Montgomery, Alabama, for complement-fixation and neutralization tests, the results of which are presented in Table 1. The complement-fixation tests were negative for western equine encephalomyelitis, St. Louis encephalitis, lymphocytic choriomeningitis and

mumps; in Case 1, the third serum specimen was negative for herpes simplex as well.

Discussion

Since immunologic crossreactivity has never been convincingly demonstrated for eastern equine encephalomyelitis[18-21] the serial rise in antibody titer by both neutralization and complement-fixation tests makes the diagnosis virtually certain. It is of interest that neither patient admitted to any direct exposure to sick horses; no members of either family and no infants or children were ill in their immediate neighborhoods. Also, although Case 1 had a history and clinical course closely approximating other descriptions,[8,22] he never had more than 141 white cells per cubic millimeter in his spinal fluid, 60 per cent of which were lymphocytes. Case 2, although mildly confused and somnolent for several days, was chiefly bothered by vertigo, nausea and ataxia.

Table 1. *Serial Antibody Titers for Eastern Equine Encephalomyelitis.*

Patient	Date of Sample	Complement Fixation	Neutralization Index
(Case 1)	9/26/55	<1:2	214
	10/10/55	++ at 1:2	320
	11/21/55	1:8	1450
(Case 2)	9/26/55	1:8	320
	10/18/55	1:16	670
	11/29/55	1:64	1450

To suggest that these cases are atypical assumes a knowledge of the clinical variants of the disease, host population, vectors, routes of entry, factors responsible for resistance and mechanism of human immunity and its correlation with the presence of neutralizing or complement-fixing antibodies. Needless to say, such data are not available. Several of the first human cases of equine encephalitis had direct contact with sick horses.[2,6] Getting,[12] in a summary of the 1938 Massachusetts epidemic, mapped out the geographic distribution of reported cases in horses and human beings. He related them to the distribution of several species of mosquitoes collected during the following summer in which experimental transmission of the virus was carried out. He pointed out that almost all the cases occurred in those most susceptible to multiple insect bites — namely, infants and children who played outdoors during an unusually wet summer. During 1939, 114 serum samples were collected by the Massachusetts Department of Public Health and included 58 from contacts of patients with eastern equine encephalomyelitis, 37 with a variety of central-nervous-system diseases, 8 with a history of an acute encephalitis more than one year previously and 11 from veterinarians who had had contact with sick horses. None had antibodies for eastern equine encephalomyelitis.[23] The assumption of horse-to-human transmission via mosquitoes was questioned by a series of recent studies[24-30] showing that the period of viremia in horses during which mosquitoes could obtain enough virus by biting was very brief. The authors believed that birds were a more likely reservoir. However, in a serologic survey of 215 pheasant farmers and handlers after a severe epidemic of eastern equine encephalomyelitis in Connecticut pheasants, no positive complement-fixation tests were found.[31] Although frequently suggested, the surmise that complement-fixing antibodies were present in a human community after an epidemic was not confirmed until 1949, when Eklund et al.,[32] studying an outbreak of human and equine forms of the disease in the Dominican Republic, showed that the highest percentage of positive serologic tests in asymptomatic human beings and horses was found near the center of the epidemic.

Studies of the pathogenesis of equine encephalitis in mice[33] have indicated that the duration of viremia is longer in younger animals, perhaps thus explaining their increased susceptibility. The pathway of spread of virus from the periphery to the spinal cord and brain via peripheral nerves or olfactory bulbs or by way of the blood stream has not been settled. The available evidence suggests no explanation for the frequently observed spotty, asymmetrical distribution of the lesions. Schlesinger[34,35] showed that the immunity of mice to challenge doses of equine encephalitis depended on the rate of virus multiplication and the size of the dose; mice previously vaccinated showed a larger and more rapid rise in both serum and central-nervous-system antibody.

Finally, one wonders if the infrequency of the human form of the disease is not more apparent than real. Serial serum analysis is not routinely performed in all cases of obscure infection associated with mild confusion or seizures. Moreover, a delay, as well as incorrect storage, may be responsible for many of the negative serologic tests. In fatal cases, special technics are required for virus isolation, and few pathology laboratories can establish a diagnosis on histologic appearance alone.

Summary

Two cases of eastern equine encephalomyelitis diagnosed by neutralization and complement-fixation tests are reported. The literature to date is briefly reviewed.

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URINARY EXCRETION OF THE SEROTONIN METABOLITE, 5-HYDROXYINDOLEACETIC ACID, IN VARIOUS CLINICAL CONDITIONS*

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CONSIDERABLE interest is being given to the possible role of serotonin (5-hydroxytryptamine) in various physiologic and pathologic processes. This amine is found primarily in the gastrointestinal tract, blood platelets and brain of mammalian species.[1-4] Although the physiologic role of serotonin is unknown, it is a potent stimulant of smooth muscle in the gastrointestinal tract, bronchi and blood vessels.[5,6] The point has been raised that it may be involved in the maintenance of normal intestinal motility[7] and in hemostasis.[8-10] The amine has also been considered a hormone regulating the circulation and function of the kidney.[5] On the basis of the observation that lysergic acid diethylamide, a potent hallucinogenic agent, antagonizes certain effects of serotonin on smooth muscle in vitro,[11] the notion has been expressed that serotonin has an important role in brain function.[12,13] It is of interest that reserpine, an agent widely used in the treatment of hypertension and neuropsychiatric disorders, has been shown to release serotonin from the three major body depots in animals, suggesting that serotonin has an important effect on brain function, possibly as a neurohumoral agent.[14-16]

Previous studies in this laboratory have shown that serotonin is derived from the essential amino acid, tryptophan, and is rapidly metabolized by the enzyme, monoamine oxidase, to 5-hydroxyindoleacetic acid, which is excreted in the urine.[17,18] The urinary excretion of 5-hydroxyindoleacetic acid serves as an easily measured index of this metabolic pathway.

The importance of excess serotonin in the syndrome characterized by valvular heart disease, asthma, diarrhea and vasomotor disturbances in patients with metastatic carcinoid tumors has recently become apparent. Studies on several such patients have revealed a marked increase in the level of blood serotonin and in the urinary excretion of its metabolite, 5-hydroxy-

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indoleacetic acid.[19-21] Because of the multiple system involvement in the "carcinoid syndrome" and speculations of possible roles for serotonin, mentioned above, it seemed worth while to study the urinary excretion of this metabolite in a variety of clinical conditions and after the administration of reserpine.

Subjects and Methods

Twenty-four-hour specimens of urine were obtained from 9 normal subjects and 72 hospitalized patients with various diseases. Usually, several specimens were obtained for analysis. Collections were also made from 2 normal subjects, who received 29 mg. of reserpine intramuscularly in divided doses over a period of five days and from 4 hypertensive patients who received 1 mg. of reserpine intramuscularly each day for eleven to fourteen days. The method used for the measurement of 5-hydroxyindoleacetic acid was that described by Udenfriend et al.[22]

Results

The results of this study are summarized in Table 1. The daily excretion in 9 normal subjects was 2.1 to 5.2 mg., and numerous specimens from elsewhere in patients whose diagnoses were in doubt fell within a range of 2.0 to 9.0 mg. As previously described, the urinary excretion in patients with the "carcinoid syndrome" was greatly elevated, being 51 to 580 mg. a day. Patients with other diseases excreted 5-hydroxyindoleacetic acid in a range of 2.0 to 9.3 mg. except for the following: 1 patient with gout, 11.0 mg.; 1 patient with Wegener's granulomatosis, 1.3 mg.; 1 patient with rheumatoid arthritis, 1.4 mg.; 4 patients with lupus erythematosus disseminatus, 1.4, 1.5, 1.6 and 1.9 mg.; 1 patient with rectal carcinoma with liver metastases, 1.0 mg.; and 1 patient with Hodgkin's disease, 1.5 mg. In the 6 subjects who received reserpine, the average control value was 6.1 mg., and the average value after reserpine administration was 6.6 mg.

Discussion

Up to the present time, it appears that a greatly elevated excretion of 5-hydroxyindoleacetic acid is specifically associated with the "carcinoid syndrome." The significance of the low levels of excretion in 6 patients with collagen vascular diseases is difficult to interpret since other patients in this group excreted normal amounts.

Since reserpine liberates serotonin, it was logical to consider the possibility that the serotonin urinary metabolite would be increased after the administration of reserpine in man. Shore et al.[14] showed that this actually happened when reserpine in a dosage of 3 to 5 mg. per kilogram of body weight was administered to animals, resulting in an increased excretion of 5-hydroxyindoleacetic acid for as long as twenty-four hours. These investigators also demonstrated in animals that this dosage of reserpine significantly lowered the serotonin level in the gastrointestinal tract as well as in the blood platelets and brain.[15,23,24] When reserpine was administered to man in a dosage of 1 to 6 mg. daily, the excretion of 5-hydroxyindoleacetic acid was not significantly altered. However, comparable doses of reserpine (30 microgm. per kilogram of body weight) lower serotonin levels in the blood platelets of man and in the blood platelets and brain of animals, but not significantly in the gastrointestinal tract.[25] Since the gastrointestinal tract is the largest depot of serotonin,

Table 1. *Urinary Excretion of 5-Hydroxyindoleacetic Acid.*

Diagnosis	No. of Patients	Urinary Excretion* mg./24. hr.
Normal subject	9	4.7, 5.2, 4.8, 4.3, 3.6 2.1, 3.3, 4.7, 4.5
Carcinoid syndrome	11	580, 572, 392, 350, 285 280, 185, 140, 76, 70, 51
Essential hypertension	10	5.4, 5.3, 5.4, 3.3, 5.6 4.5, 7.0, 6.2, 5.1, 8.4
Idiopathic thrombocytopenic purpura	2	7.4, 2.7
Schizophrenia	4	2.2, 4.5, 2.8, 6.7
Congenital pulmonic stenosis	1	6.4
Postoperative paralytic ileus	1	4.5
Rheumatic heart disease	2	7.1, 5.3
Gout	1	11.0
Laënnec's cirrhosis, with Eck fistula	1	9.2
Renal calculi	1	3.6
Hypoparathyroidism	1	5.1
Hyperparathyroidism	1	4.8
Hypothyroidism	3	2.2, 2.0, 3.4
Porphyria	3	6.9, 3.8, 3.6
Eclampsia	1	4.6
Episodic blushing	1	3.6
Duodenal ulcer	1	4.4
Arteriosclerotic heart disease	1	4.5
Ulcerative colitis	1	3.7
Wegener's granulomatosis	1	1.3
Rheumatoid arthritis	3	2.3, 1.4, 2.5
Lupus erythematosus disseminatus	8	2.0, 1.4, 1.5, 1.6, 1.9 9.3, 6.7, 3.6
Acute rheumatic fever	1	7.5
Scleroderma	1	5.1
Multiple myeloma	3	5.5, 3.7, 5.6
Leukemia	1	4.0
Lymphoma	3	3.7, 9.0, 1.5
Metastatic melanoma	2	2.6, 3.3
Rectal carcinoma, with liver metastases	1	1.0
Ovarian carcinoma	1	2.1

*Values represent average of multiple determinations in each patient.

quantitative measurement of 5-hydroxyindoleacetic acid excretion may not detect alterations of serotonin metabolism unless this depot is affected or there is a marked overproduction of serotonin by a secreting tumor. Thus significant changes may occur in serotonin levels of platelets and brain without being associated with a detectable alteration in the urinary excretion of 5-hydroxyindoleacetic acid.

Summary

The urinary excretion of 5-hydroxyindoleacetic acid in patients with various clinical conditions was unequivocally elevated only in the presence of metastatic carcinoid tumors. Low values were found in 6 patients with collagen vascular disease. Reserpine, in a dosage known to lower platelet serotonin, did not change the excretion of the serotonin metabolite.

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SPECIAL ARTICLE

CHEMICAL CONTROL OF PULMONARY VENTILATION*

II. Hypoxia and Respiratory Acclimatization

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THE strange phenomena observed during a stay in high mountains attracted attention long before even the most elementary bases of respiratory physiology had been laid down by Lavoisier and Spallanzani. In the present age, in which airplanes take man easily to heights previously undreamed of, there is an infinitely greater interest in these problems. The conquerors of the highest of the earth's peaks have shown that man can become adapted to altitude conditions that would soon kill him if he were suddenly exposed to them. I cannot trace the historical aspects of this problem, which is surely among the most interesting in physiology. I shall take as my starting point the recognition by the French physiologist, Bert,[1] that all these phenomena can mainly be referred to oxygen lack, which is designated as *"hypoxia."* If this supposition is correct it does not matter how the hypoxia has been produced. Innumerable experiments have shown that apart from secondary phenomena this idea is correct. One can therefore study the matter under widely differing conditions, provided that the common factor of oxygen lack is present. The first and most striking sign consists of increased pulmonary ventilation, which is called hyperpnea and whose biologic purpose is obviously to make more air and therefore more oxygen pass through the lungs, to compensate for the oxygen lack. In fact such hyperpnea occurs under a variety of conditions of oxygen lack, including climbing a high mountain, being taken up in a nonpressurized air-

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plane, entering a low-pressure chamber or, finally, breathing a mixture of gases at ordinary atmospheric pressure but containing diminished oxygen.

Mechanism of Hypoxia

One immediately wonders how the lack of a substance can act as a stimulus. How is it possible that a material can be effective on account of its absence or at least its reduction? This was the question that the great German physiologist Pflüger[2] asked nearly ninety years ago, and, in essentials, answered. This action is possible only because incompletely oxidized compounds are produced during oxygen lack, causing the excitatory effect. Forty-five years ago, when I attempted to refer the excitatory effect of both carbon dioxide and oxygen lack to a single shared factor, I believed that this could be found in increased hydrogen ion concentration. I was led to this view because many experiments had shown that acidic substances, especially lactic acid, are produced during oxygen lack. Carbon dioxide, as well as increased production of acid, will, of course, lead to a rise of hydrogen ion concentration. But some years later, when I made the first direct measurements of the pH of the blood during oxygen lack, I found on the contrary that the reaction of the blood shifted toward the alkaline and not toward the acid side. The explanation seemed to me simple: these stimulating acidic substances were produced first of all in organs that, since the chemoreceptors had not yet been discovered, seemed to be especially sensitive to oxygen lack — namely, the centers. This occasioned an increase in ventilation that, by washing out the carbon dioxide, led to a secondary shift of blood pH to the alkaline side.

A discussion of this mechanism must be left to my third lecture. For the moment it is sufficient to keep in mind the following curious situation: on the one hand the activity of the respiratory center parallels the carbon dioxide pressure or the hydrogen ion concentration, a fact that is questioned by no one; and, on the other, oxygen lack, to augment the oxygen supply, increases pulmonary ventilation, but this in its turn, by washing out carbon dioxide and so decreasing the hydrogen ion concentration, helps diminish pulmonary ventilation. The organism is, in a sense, working against itself — it is lessening the effectiveness of the measures that it has taken. How is it possible that something so apparently contradictory can happen?

Pulmonary Ventilation

To understand this paradox one must approach the problem of pulmonary ventilation as a whole from the standpoint of modern research. Pulmonary ventilation has two tasks: to ensure the equilibrium between oxygen demand and oxygen supply and, secondly, to regulate the acid-base equilibrium, which normally can be expressed in terms of pH. To carry out the first task, as I tried to show in my first lecture, the organism has developed the chemoreceptor mechanism, which shows an extreme sensitivity to changes in oxygen pressure. And the chemoreceptor drives produced by these changes control the oxygen pressure in the centers in such a way that it is maintained at a level that is not too high and, above all, not too low.

The second task — namely, the maintenance of the acid-base equilibrium — is, as I hope to show in my next lecture, accomplished chiefly through an extraordinary sensitivity of the centers themselves to any change in pH. Under ordinary conditions the two tasks are combined without interference of one with the other. But there is one exception: acute hypoxia. If for any reason a pH change originates hematogenically in the blood itself — for example, by a metabolic acidosis or alkalosis — the organism regulates this upset by a change in pulmonary ventilation. If the hydrogen ion concentration is too high, ventilation is increased, and more carbon dioxide is washed out, so that the hydrogen ion concentration is decreased. If on the other hand, hydrogen ion concentration is too low, ventilation is reduced, and carbon dioxide is retained so that the pH decreases. However, with oxygen lack, primarily, there is no disturbance of pH, which if it is to be kept constant demands constancy of lung ventilation. In such a case oxygen supply would be insufficient. But if the ventilation is indeed increased to augment the oxygen supply, a disturbance of the acid-base equilibrium inevitably follows, as stated above. And this disturbance not only will antagonize the compensation but also can cause a great number of other upsets in the organism. What can the organism do in this situation of stress? A disturbance of the acid-base equilibrium can be tolerated for considerable periods, but lack of oxygen cannot. Therefore, first of all, the lack of oxygen must be remedied, cost what it may. Later, other measures can be taken to reduce the acid-base disturbance as far as possible. These mechanisms are indeed what have been designated as *respiratory acclimatization*. The complexity of interaction between these mechanisms, a complexity chiefly due to the co-operation of glomerogenic and central drives, has only recently been discovered and is still a topic of controversy. I should like to describe this complex series of events.

Respiratory Acclimatization

Again, the best plan is to start with experiments on animals, because, as I explained in the last lecture, only in this way is it possible to differentiate clearly glomerogenic and central drives. This is done by cold blocking of the sinus nerves after removal of the other chemoreceptors. First of all to be considered is *acute* hypoxia, in which the duration of oxygen lack is twenty minutes as a maximum. In this connection

the experiments of the Danish physiologist Bjurstedt[3] are of special importance. Using narcotized dogs with severed vagus nerves, he investigated under conditions of hypoxia, on the one hand, the changes in pulmonary ventilation and, on the other, the changes in oxygen saturation and pH of the blood.

Figure 1 gives a good example of such an experiment. Blocking of the sinus nerves (Fig. 1*A*) produces distinct decrease of ventilation during breathing of ordinary air. This decrease diminishes quickly, clearly because the accompanying increase of carbon dioxide pressure and hydrogen ion concentration will augment the central drive. Indeed, as soon as the block is removed, ventilation increases above its initial level. In B, in which 8.2 per cent oxygen is breathed, the decrease at the onset of blocking is much more drastic. Here, the central drives alone can only maintain the ventilation at one quarter of its normal magnitude. Here, too, and in a much more striking fashion one sees a quick restitution of respiration, owing to the decrease of carbon dioxide excretion and of pH, which stimulates the respiratory center. This is clearly shown by the pH curve in tracing B. If the hypoxia is continued for twenty minutes, because of the strong shift of the blood pH toward the alkaline side the centers are no longer able to maintain respiration by themselves. This is clearly shown in C, where cold block of the chemoreceptors leads to a complete cessation of ventilation. This persists in spite of the rapidly increasing acidity and can only be remedied by artificial respiration. Thus, in acute hypoxia the control of respiration is transferred in a progressively increasing fashion to the chemoreceptor mechanism, so that after a short while ventilation is 100 per cent of glomerogenic origin. Under these circumstances the center alone cannot maintain respiration. If the chemoreceptor drives are removed, respiration ceases, and death by suffocation follows.

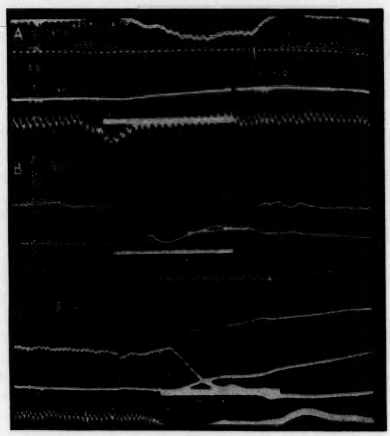

FIGURE 1. *Cold Blocking of the Sinus Nerves (after Bjurstedt[3]).*

Besides his studies on acute hypoxia Bjurstedt[3] performed experiments in which the hypoxia lasted for several hours, providing fundamental knowledge about *chronic* hypoxia. If the hypoxia produced by breathing of air with 8 to 11 per cent oxygen lasted six to ten hours, the blood pH in his experimental dogs, which at first had shifted strongly to the alkaline side on account of the hyperpnea, now gradually shifted back to its normal level. In my last lecture I discussed the remarkable fact that, on the one hand, the activity of the central drive parallels the hydrogen ion concentration of the blood, whereas, on the other hand, for reasons not yet definitely established, the effect of the chemoreceptor drive is just the reverse in the sense that the more alkaline the blood, the greater the effect. Corresponding with this, during hypoxia lasting several hours, the effect of cold blocking of the sinus nerves becomes less and less. The ventilation no longer depends completely on the chemoreceptors as it did at the beginning. In spite of the persisting increase of respiration, the central drive takes over control more and more. What is being considered here is nothing but the beginning of high-altitude acclimatization, which, surprisingly enough, starts after the lapse of even a few hours. The same principle holds true for human beings.

It was known long ago that in man lowering of oxygen pressure produced by whatever method had as its first and most important effect an increase in ventilation. What is the oxygen pressure at which hyperpnea starts? Haldane and his collaborators,[4] who were the first to study this in detail, maintained it to be at a level corresponding approximately to a height of 3000 meters, or 9000 feet. But Haldane[5] himself made the observation that the initial hyperpnea increases for a time during a longer stay at high altitudes, and he found the correct explanation — namely, that the initial shift of the acid-base equilibrium to the alkaline side gradually decreased, just as Bjurstedt found that, in spite of the persistence of hypoxia and hyperpnea, the blood pH returned to its normal level. How is this achieved?

To clear up this point, which is indeed the focus of the whole problem of acclimatization, I shall have to make a short excursion into the physical chemistry of the blood. Carbon dioxide is present in the blood in two forms: carbon dioxide, or carbonic acid, and as bicarbonate chiefly with sodium ions but also with others that are of no interest to us. The problem can be limited to the bicarbonate ion. The ratio of carbonic acid to bicarbonate, under normal circumstances, is about 3:60. This means that 100 ml. of

blood contains 3 ml. of carbonic acid and 60 ml. of bound carbon dioxide. It is by this ratio that the reaction of the blood is determined, as was shown more than forty years ago by Henderson,[6] the outstanding physical chemist at Harvard. This is expressed in the famous Henderson equation, which, leaving out the basic ion, can be expressed as follows:

$$cH = K\frac{[H_2CO_3]}{[HCO_3^-]} .$$

Now as I said at the beginning, one of the primary functions of pulmonary ventilation is to keep the blood reaction constant. If the hydrogen ion concentration is increased, respiration increases too, and more carbon dioxide is washed out so that the hydrogen ion concentration falls. If the hydrogen ion concentration decreases, respiration is also reduced, more carbon dioxide is retained, the numerator in the equation becomes greater and the cH is brought to its normal level. But in hypoxia life itself demands that the increase in respiration be maintained. Thus, a lowering of hydrogen ion concentration — that is, a respiratory alkalosis — is produced that cannot be corrected by reduction of ventilation; this means the numerator of the equation cannot be increased. What can the organism do? It changes the denominator. The numerator has become less; therefore, the denominator must also become less. This is produced by a loss from the blood of bicarbonate, of course, with the corresponding basic ions, which partly migrate from the blood to the tissues and partly go out of the organism by way of the kidneys. The essentials of *acclimatization* consist in nothing more than the migration of alkali from the blood and the shift of the hydrogen ion concentration toward normal, thus restoring more or less the normal acid-base equilibrium.

This acclimatization takes place in the following stages: in the first phase of hypoxia increased ventilation is produced by excitation of the glomera but cannot reach its maximum effect on account of the shift of the blood cH toward the alkaline side, which works against it; the second phase, which, as I have already pointed out, after a few hours consists of migration of bicarbonate from the blood, decrease of alkali reserve, increase of cH, a further augmentation of ventilation and a further lowering of alveolar carbon dioxide pressure. This increase of ventilation, with its consequent decrease of alveolar carbon dioxide pressure, continues for about four to ten days, by which time a new equilibrium will have been approximately established in the Henderson equation, in which the decrease of the numerator has been compensated for by a decrease of the denominator. This approximation to the normal level of the pH goes hand in hand with important changes, which Bjurstedt[3] recorded in his cold-block experiments, as already mentioned. The control of respiration, which at first, according to the degree of oxygen lack, was taken over by the chemoreceptors, even to the extent of 100 per cent, now, as the pH approaches normal again, is once more taken over predominantly by the respiratory center. This phenomenon can also be demonstrated in human beings. Since the exciting agent for the chemoreceptors under these conditions is lack of oxygen, one can exclude its effect by making the subject of the experiment breathe 100 per cent oxygen. The effect is completely different according to whether it is done in the first, or acute, phase of hypoxia or in the chronic, or second, phase after acclimatization. In the first phase the volume of respiration falls precipitously. Indeed, in flyers at high altitude, it has been reported that when 100 per cent oxygen is breathed after strong hypoxia, respiration may cease suddenly, leading to unconsciousness and cramps. The action of the chemoreceptors, which were in 100 per cent control of respiration, has suddenly been eliminated, and the respiratory center, bathed in a markedly alkaline blood, has lost its automatic capacity for action.

In the same way two other peculiar phenomena can be explained. When the automatic activity of the respiratory center is reduced — for example, during sleep — and if at the same time there is oxygen lack as in high mountains, the phenomenon of periodic respiration is often observed in unacclimatized persons. A few deep breaths cause the chemoreceptors, which are chiefly in control of respiration, to reduce their activity, and respiration stops. This continues until the oxygen lack so produced sets it in motion again. The breathing brought about in this way cuts out the chemoreceptors again, respiration stops, and the whole procedure is repeated. I remember that, on waking up on the day after my ascent to the Capanna Margherita, situated at about 15,000 feet on the Monte Rosa in Switzerland, I was able to observe this periodic respiration splendidly in myself.

The situation is quite different in the acclimatized person. When he suddenly breathes 100 per cent oxygen there is scarcely any effect. Respiration, which has achieved independence from the chemoreceptors, shows little reduction. One can thus explain the second remarkably peculiar effect that anyone can see for himself when he returns to normal altitudes after a few weeks' stay in high mountains: the alveolar carbon dioxide remains at a low level for a considerable time, thus showing that the increase of respiration continues although there is no oxygen lack. This means that the increase of respiration, though originally caused by oxygen lack, has become independent of it. Indeed, respiration remains high until the alkali reserve has returned to its normal level — that is, until not only the numerator-denominator ratio of the Henderson equation but also their *absolute* values have been attained. This is sometimes a matter of weeks.

Discussion

But now the chief problem of chronic hypoxia presents itself. How is it possible for a decrease in value of the Henderson equation (I repeat, not the ratio but the absolute values of the numerator and denominator) to cause the increase of ventilation necessary to compensate for oxygen lack, without noticeable activity of the chemoreceptors? In proposing a solution of this problem — a solution that has not yet found general acceptance — I must return again to fundamentals. As I said at the beginning of this lecture, the fact of increase of respiration in hypoxia was known long ago. The earlier authors did not need to bother with the chemoreceptors because they had not yet been discovered; most of them were of the opinion that respiration was controlled by carbon dioxide. But even they knew that in oxygen lack the carbon dioxide pressure is not increased. They found what they considered an excellent solution for this: in oxygen lack the excitability of the respiratory center to carbon dioxide is increased — hence the increase in ventilation in spite of decreased carbon dioxide pressure. What a magnificent idea — all difficulties swept away! This so-called explanation was proposed as long as seventy-five years ago by Hermann[7] and by Zuntz.[8] Later, it was adopted by Haldane[5] in England and by Lindhard[9] in Denmark, and it has persisted up to the present; this concept is in the reports of Nielsen[10] in Copenhagen, Gray[11] in Chicago and so on.

What is this magic formula that solves all the puzzles? One of my hobbies is the analysis of concepts, which are the working tools of the scientist. Inexactitude in concepts seems to me for the scientist just as dangerous as dirtiness in instruments for the surgeon. One should define explanation and also excitability. Everyone agrees that it is the function of science to explain natural phenomena. But how is this achieved? I do not want to start manipulating causality, which itself is never quite clear. I think the best definition was given by a man who was not only a great physiologist (he discovered the function of the labyrinth) and not only a great physicist (his ideas approximated those of Einstein) but also a great philosopher, although he himself would have denied it. I refer to Ernst Mach, of Vienna. He stated that the function of science was *mentally to reproduce the facts in the simplest and most economical way.* Now, what sort of mental picture can one gain of the facts using the concept of excitability? The concept of excitability, irritability, sensitivity was introduced into physiology by the British anatomist Glisson in the seventeenth century. It was believed that in this way a characteristic property of the living as opposed to the nonliving world could be defined in that insignificant external changes had large effects of a disproportionate magnitude. The concept is rarely used in this absolute sense because explosive materials, for example, show the same thing to a much greater degree. In this absolute sense it is only used to distinguish living from dead organisms or organs; these may or may not remain excitable. There is no objection against this usage. But the field of application is much larger for the *relative* magnitude of the effects of stimulation. Every observation shows that the same external change under different conditions has an effect of different magnitude, sometimes larger and sometimes smaller. As a corollary, if it is desired to achieve an effect of a certain magnitude an appropriately adjusted stimulus must be applied. Under these circumstances one says that the excitability has increased or decreased respectively. This is a short, expedient way of describing a set of observed facts. But does this descriptive method really explain anything in the sense of a mental picture of what has happened? When I say that an anesthetized nerve has a reduced excitability I indicate that a stronger stimulus must be used for the same effect. But have I said anything at all about the nature of narcosis? Obviously not. In the same way, when I observe that a lower carbon dioxide pressure is sufficient to produce the same increase in ventilation during hypoxia, I can express this fact equally well with the statement that the center has an increased excitability to carbon dioxide. But I have explained precisely nothing. This is but another method of expressing the same observed fact. It is not the increased excitability that produces increased ventilation — on the contrary, it is my observation of increased ventilation that leads me to say that the excitability of the center has increased. I have established a fact but I am just as able or unable to reproduce the process mentally. In addition it is false to assume that anything has been revealed about the general conditions of the respiratory center as is usually believed. If carbon dioxide has an increased effect during oxygen lack this does not necessarily mean that other stimuli will behave in the same way. For example, certain narcotic drugs strongly decrease the excitability to carbon dioxide whereas the excitability to the hypoxic effects of the chemoreceptors or other reflexes remains the same. But to stick to the excitability to carbon dioxide, why does carbon dioxide have a greater effect during oxygen lack?

Nothing seems to me easier than to find such a real explanation provided one accepts a premise: the erroneous conception that carbon dioxide is a specific respiratory stimulant (a conception that is still widely accepted today) must be abandoned, and replaced by the theory that chemical control of respiration is achieved through hydrogen ion concentration, a theory to which I shall devote my third lecture.

To return to the Henderson equation: according to the theory advanced above, respiration depends not on the numerator — that is, the carbonic acid concentration — but on the cH. If one adds a certain amount of carbon dioxide to the inspired air, this in-

creases the value of the numerator and so the cH, which in its turn increases the ventilation. I have demonstrated how hyperpnea during oxygen lack decreases the numerator by washing out the carbon dioxide. If the same amount of carbon dioxide as was present before is added, it is clear that this must cause a greater increase in hydrogen ion concentration than in the previous case. Therefore, the increase in respiration will be greater than that under normal conditions or, to express the same thing in other terms, the respiratory center has become more excitable to carbon dioxide during hypoxia. This essential situation is not changed, even when migration of bicarbonate during high-altitude acclimatization has restored the equilibrium between numerator and denominator, so that the pH has returned more or less to its normal level. To give a mathematical illustration: as I have mentioned, the H_2CO_3/HCO_3^- ratio of carbonic acid to bicarbonate is, under normal conditions, approximately 3/60. If the numerator is increased by the addition of carbon dioxide to the inspired air in a proportion of 3:1, the fraction becomes $(3+1)/60$, so that the hydrogen ion concentration has increased from 3/60 or 1/20 to 4/60 or 1/15. Now, if, because of oxygen lack, the absolute value has changed from 3 to 1, at the same time on account of the compensatory bicarbonate emigration the denominator will have fallen from 60 to 20. The former value of the fraction was 3/60; the new one is 1/20. So the value of the cH has reached its former level. But if I now add the same excess of carbon dioxide I shall get $(1+1)/20$ — that is, 2/20 or 1/10, instead of 1/15 in the former case under normal conditions. This increased hydrogen ion concentration value will lead to increased ventilation. I have deliberately chosen figures that are simplified and exaggerated for the purpose of demonstrating the principle. Accordingly, there is nothing miraculous in the increased sensitivity to carbon dioxide — indeed, if it had not been demonstrated experimentally, it could have been predicted from the Henderson equation. Thus, mental insight into the observed phenomenon has been gained, and the phenomenon has been explained.

But the explanation includes something else: what is true for an artificial addition of carbon dioxide must, of course, be equally true for the natural carbon dioxide increase continually produced by metabolism. Metabolism during oxygen lack is the same as or even greater than usual, as has been observed a number of times. Thus, here, too, when the absolute value of the Henderson equation has been diminished by acclimatization, the increase of hydrogen ion concentration and therefore of ventilation must be greater than under normal conditions, and ventilation must continue to be increased without interference from the chemoreceptor mechanism. This is exactly what has been observed. And so, indeed, it has also been possible to explain the persistent increase of respiration during chronic hypoxia — an increase that does not depend any more on the chemoreceptor excitation.

To the worshippers of carbon dioxide this seems far too simple. They cling to the specific effect of the gas and the specific excitability of the respiratory center to it. They try to prove this by saying that if everything is a simple consequence of hyperpnea, it should also be observed during acidosis such as that caused by ammonium chloride, which produces a strong shift of the blood pH toward the acid side accompanied by hyperpnea. Now, using this substance, Nielsen[10] in Denmark, Loeschcke and his collaborators[12] in Germany and, more recently, Stroud[13] in Rochester all proved that oxygen lack has a much greater effect on carbon dioxide excitability than this acidosis. But the conditions in ammonium chloride acidosis are peculiar and specific, so that a comparison of the two is quite impossible. In experiments recently carried out,[14] which I shall mention in more detail in my next lecture, it was established that although the reaction of the blood was shifted very strongly to the acid side, that of the cerebrospinal fluid was strongly shifted to the alkaline side. The effects of ammonium chloride on pulmonary ventilation represent the algebraic sum of these two opposing factors. But there is another method by which the situation in hypoxia can be faithfully reproduced although no oxygen lack occurs. This way was recently followed by Brown[15] in Minnesota. He showed that hyperventilation of a human subject for twenty-four hours lowers alveolar carbon dioxide pressure, shifts blood pH toward the alkaline side and increases excitability to carbon dioxide of the same order as that observed during oxygen lack. Even if the figures do not always agree exactly, the explanation, as Brown rightly observes, can lie in the fact that the buffering capacity of the blood may be different from that of the cells of the respiratory center. Starting from this point of view, he conducted a meaningful set of experiments on guinea pigs.[16] First of all he caused a hypoxic hyperpnea by exposure to reduced pressure. After some time the brains were quickly extracted, frozen, ground and then set to come to equilibrium with three different mixtures of oxygen and carbon dioxide. The changes of pH produced in this way were compared with those observed in normal animals. There was a distinct increase in effect of carbon dioxide in the hypoxic brain pulp, proving that a simple physicochemical process is involved. But, in the usual terminology, this would mean that the carbon dioxide excitability of the brain substance had increased.

The result of these experiments provides, perhaps, an approach to the understanding of a phenomenon of high-altitude acclimatization that has not yet been explained. On the heights there is an increase

of sensitivity not only to carbon dioxide but also to lack of oxygen. It can be shown that if an unacclimatized person and an acclimatized person are suddenly subjected to strong oxygen lack, the increase of ventilation in the latter is much greater than that in the former. The greater the increase of pulmonary ventilation, the greater the possibility of enduring lack of oxygen, which is the most important factor for those who wish to climb to very high altitudes. Luft and Opitz,[17] in experiments on the behavior of both unacclimatized and acclimatized persons in the low-pressure chamber when exposed to a simulated height of about 28,500 feet, found that their subjects showed in Berlin at this simulated altitude the severest symptoms between two and a half and three minutes, including unconsciousness and cramps. However, the same persons, after a stay of several weeks on the Jungfraujoch at a height of more than 11,300 feet, were able to endure twenty minutes of the same treatment without difficulty. In this case it is clear that one cannot be concerned with acclimatization of the center, but with an effect of the glomera, since these are the only structures that react to sudden oxygen lack.

In the next lecture I shall demonstrate that the excitation of the glomera also depends on the pH present in them. When it is understood that in the protoplasm of the glomus cells, in the same way as in the centers, a reduction of buffering capacity would take place on account of bicarbonate migration, it is apparent that an increased sensitivity against pH-changing factors such as oxygen lack would be produced. This, in its turn, helps explain how the increase of respiration depends on chemoreceptor excitation.

On the basis of the researches performed up to the present I have endeavored to give a picture of the physicochemical processes that take place during hypoxia and acclimatization. Changes of oxygen pressure, of carbon dioxide pressure and of pH interact in a complex and interlocking way. Must each of these factors be considered separately? Is this really the simplest and most economical mental approach to these phenomena, which according to Mach is the task of science? Or is it possible to find a more economical form of regarding these different mechanisms, which attempts to reduce them to a single basic factor? This question I intend to discuss in my last lecture.

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MEDICAL PROGRESS

ANESTHESIOLOGY

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IN an unprecedented way recent years have seen a co-ordination of effort in an attempt to push forward surgical frontiers. Pioneering has been shared by experimental and clinical surgeons and internists alike, with physiologists and pharmacologists striving to acquire more effective and safer agents and methods and to gain a better understanding of the action of the older ones. In this ceaseless quest, which at times seems to carry an almost breathless urgency, the anesthesiologist continues to occupy an intermediate position. If, among medical specialties, anesthesiology can be said to be "neither fish nor fowl," the anesthesiologist can with equal truth be described as "being all things to all men." The anesthesiologist is often the translator of these basic discoveries into better surgical care for patients.

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The surgical invasion of hitherto inaccessible organs such as the heart and the aorta not only has posed new technical problems to the anesthesiologist but also has demanded an appreciation of basic physiology in a way undreamed of a few years ago.

As always, investigation in the field of anesthesiology is directed toward the development of agents, and methods for their administration that will cause fewer and less profound disturbances of normal physiologic function. In addition, this quest includes a search for ways to help the body better withstand the inevitable physiologic insult of anesthesia and surgery. The purpose of this discussion is to summarize some of the "progress" that has been made in the search for these better ways of helping the human organism to compensate for the inescapably heavier blows that must be dealt its physiology as the field of definitive surgery is enlarged. This of necessity includes some subjects that can hardly be considered new, as well as some that are, perhaps, too new. None will be mentioned that have not been demonstrated to have at least some clinical significance.

Muscle Relaxants

For simplicity, the muscle relaxants can be divided into two groups according to their mode of action, though the dividing line is not always a distinct one and the agents of one group may at times seem to have the characteristics of the other.

The first group includes tubocurarine, dimethyltubocurarine, gallamine (Flaxedil), laudexium methylsulfate (Laudolissin) and benzoquinonium (Mytolon). These drugs have the common property of interfering with the normal action of acetylcholine released at the motor-nerve endings. They raise the threshold of the nerve plate to acetylcholine, thereby preventing the depolarization necessary to propagate the impulse to the adjacent muscle. This action may be considered one of competition with acetylcholine. In general, the anticholinesterases are antagonists to these drugs. Strictly speaking, the term "curarelike" is properly reserved for these acetylcholine-competitive inhibition-type compounds.

The second group, which includes decamethonium and succinylcholine, produces persistent depolarization at the nerve-end plate and prevents the physiologic depolarization-repolarization sequence of the normal acetylcholine-acetylcholinesterase system necessary for neuromuscular transmission. In direct contrast to the first (curarelike) group, anticholinesterase drugs potentiate the effects of this second (depolarizing) group. In theory, the first group of drugs is antagonistic to the second, even though the final effect — muscular relaxation — is the same.

A much more complete concept of the different mechanisms of neuromuscular block can be obtained from reviews of the pharmacology of the neuromuscular junction.[1-3]

Succinylcholine

In the quest for the ideal muscle relaxant the qualifications sought for are no different from those considered desirable for all anesthetic agents. These include specificity and rapid onset of action; readily controllable intensity of action; wide margin between optimal therapeutic dose and minimal lethal dose; and rapid and complete recovery when administration of the drug is discontinued. At present, probably succinylcholine most nearly meets these specifications. This compound represents an end-to-end union of two molecules of acetylcholine and is structurally closely related to decamethonium, another depolarizing-type compound. The structural similarity between succinylcholine and decamethonium and the close interrelation of acetylcholine to both have given rise to speculation on the mechanisms of action based on the structural-activity relation.[4]

Succinylcholine is rapidly hydrolyzed in man by plasma cholinesterase (pseudocholinesterase or nonspecific cholinesterase), and to a lesser extent by acetylcholinesterase (true cholinesterase). This enzymatic hydrolysis occurs in two steps. In the first, succinylcholine is hydrolyzed to succinylmonocholine and choline. Then, succinylmonocholine is hydrolyzed considerably more slowly to succinic acid and choline.[5] This intermediate succinylmonocholine has been shown to have a weak neuromuscular-blocking action.[6]

An average of less than 3 per cent of intravenously administered succinylcholine is excreted unchanged in the urine.[7] Other relaxants, excluding tubocurarine and dimethyltubocurarine, which undergo considerable degradation in the body,[8-10] are excreted almost quantitatively unchanged in the urine.[3,11,12] These agents owe their duration of action to tissue redistribution. The rapid hydrolysis of succinylcholine within the body distinguishes it from the other relaxants and accounts for its brevity of action and ease of control. No cumulative or tachyphylactic effects have been reported, and the salivation, increased bronchial secretion, bronchospasm, tachycardia and hypotension sometimes seen with other relaxants are absent.[13-16]

Succinylcholine is administered intravenously by rapid injection of 30 to 60 mg. if profound relaxation of short duration is desired. If prolonged relaxation is required, it is best administered by continuous intravenous infusion of 0.1 or 0.2 per cent in physiologic saline or 5 per cent dextrose solution. The degree of relaxation can be changed within thirty seconds by regulation of the rate of flow. When administration is discontinued, muscle tone and respiratory exchange usually return to predrug levels within two to four minutes. The rapidity of onset, brevity of action and ease of control of succinylcholine compare favorably with those of any of the other clinically used relaxants.[17]

It has been reported that succinylcholine, in doses adequate to produce surgical relaxation, may have a sparing action on the muscles of respiration.[18] Others believe that no such selective sparing action is present and that respiration is progressively paralyzed as the degree of neuromuscular block progresses.[19,20] Our clinical experience concurs with the finding that there is no selective respiratory-sparing action. We do not believe that adequate abdominal relaxation can be obtained without the need for assisted respirations.

The ease of control and brevity of action of succinylcholine have made a search for a chemical antagonist of little practical significance. On the other hand, an extender has been given brief clinical trial.[21,22] The value of an extender seems debatable since the duration of action of succinylcholine can so easily be prolonged simply by continuance of its administration.

Occasionally, an increase in blood pressure is seen with the use of succinylcholine. Some have attributed this to a decrease in respiratory minute volume with retention of carbon dioxide.[23-25] Another explanation has been that of a muscarinic-blocking effect in the presence of atropine, resulting in a stimulating effect on the autonomic ganglions.[26]

The chief complication that follows the use of succinylcholine is the occurrence of occasional prolonged apnea. Several of the early reports described apnea after single injections of the drug,[27-30] which may have been due to overdosage. Other reports of apnea after a continuous-infusion technic are not so easily explained.[31-33] The wide variation of pseudocholinesterase levels in normal patients[33,34] and the low pseudocholinesterase levels found in chronic liver disease, cachexia and patients with diminished blood volumes have been mentioned as possible etiologic factors.[23,35-37] Decrease in the period of apnea after intravenous administration of concentrated plasma cholinesterase preparations has been reported.[34,36] Others, however, have found concentrated plasma cholinesterase of no definite value in alleviating a prolonged respiratory depression after succinylcholine administration.[32,33] A central depression of the respiratory center by the drug has been suggested.[38] The possibility of persisting concentrations of succinylmonocholine has also been suggested as an explanation.[39] It was mentioned before that succinylmonocholine is an intermediary product in the hydrolysis of succinylcholine and is a weak neuromuscular-blocking agent.[6] Controlled respiration, with resulting hyperventilation, acapnia and loss of respiratory drive, must also be considered. This apnea most often occurs with patients suffering from bronchiectasis and emphysema, who unquestionably have considerable alteration in their respiratory mechanism.

Succinylcholine is probably the most valuable and widely applicable of the many muscle relaxants that have become available to the clinical anesthesiologist since the introduction of curare in 1942.[40] Its chief complication is occasional prolonged apnea or respiratory depression. As yet we are unable to point a finger at a specific etiologic factor for this complication, and it is unlikely that any one factor is responsible in all cases. As an explanation we must always consider overdosage, whether actual, owing to improper administration, or relative, owing to the decreased ability of some patients with chronic illness, inanition or diminished blood volumes to hydrolyze the drug with the rapidity seen in healthy persons. The complication is seen much more frequently in patients with chronic pulmonary disease such as emphysema. The avoidance of prolonged periods of apnea calls for vigilance in individualizing the rate of administration while depression of respiration is used as a guide to dosage. The aim should be assistance to respiration, not control.

Intravenous Anesthesia

Since the advent of the muscle relaxants, the use of thiopental to supplement the nitrous oxide oxygen sequence has come into even greater prominence.

It has been shown that the short duration of action of thiopental administered intravenously is the result of the rapid redistribution of the drug from the plasma into other body tissues, notably the fat.[41] With equilibrium established, ultimate concentration of the drug in the fat is six to twelve times that found in other tissues. Actual metabolism of the agent proceeds at a rate of 10 to 15 per cent per hour. The prolonged postanesthetic somnolence and depression seen after a large dose is accounted for by the slow rate of metabolism and the resultant slowly decreasing equilibrium between the blood stream and the large reservoir in the fat.[42] This affinity of thiopental for fat is shared in similar degree by thialbarbitone (Kemithal) and thiamylal (Surital) and also by the nonsulfur-containing hexobarbital (Evipal). Newer thiobarbiturates have been investigated in a search for a drug that is metabolized more rapidly.[44,45] Some of these drugs show a more transient action than thiopental, but this is due to a greater affinity for body fat.[45] Probably all thiobarbiturates share this plasma-fat-redistribution property, and better agents will be found in compounds other than the thiobarbiturates.

Thiopental requirements can be decreased by the intermittent intravenous administration of meperidine (Demerol), morphine, levorphanol tartrate (Dromoran) and alphaprodine (Nisentil) as additional supplements in the thiopental-nitrous oxide-oxygen sequence.[46-51] If care is taken to prevent overdosage, recovery is usually rapid, with relative freedom from nausea, vomiting and emergence delirium. Furthermore, residual analgesia often lasting for several hours may persist.

A major drawback of narcotic supplementation is prolonged respiratory depression. This depression may at times require assistance to respiration, and for this reason is not used for short procedures or near the conclusion of longer ones. A Demerol drip has been used to obtain narcotic analgesia with a minimum of respiratory depression.[52] Other technics to combat the respiratory depression inherent in narcotic supplementation include those combining a narcotic and narcotic antagonist in proper ratio to offset respiratory effects without diminishing analgesia.[53-55]

Induced Hypotension

Induced hypotension is the deliberate lowering of the systemic blood pressure in the anesthetized patient. It has as its prime purpose the diminution of bleeding, specifically capillary bleeding, in the operative field. It is usually instituted under the direction of the anesthesiologist and is presumably always reversible and under control. This hypotension is properly reserved for the surgical procedure in which blood loss is profuse or even prohibitive or for the unusual case in which even a slight ooze at a strategic moment must be avoided (in a fenestration operation).[56] The technic finds its widest application in surgical treatment of vascular malformations and tumors of the brain.[57,58] It has also been employed for extensive block resections for cancer, such as pelvic evisceration[59] and for venous-shunt surgery.[60]

The several factors that combine to maintain normal arterial blood pressure include the pumping action of the heart, the quantity of blood in the arterial system, the viscosity of the blood, the elasticity of the arterial walls, and the peripheral resistance.[61] Of these five factors, three are relatively unalterable. The elasticity of the arteries is an inborn constant, at least over the period occupied by any surgical procedure. The viscosity of the blood, although it may change during operations in response to drugs, trauma, blood loss and fluid replacement, does not lend itself to control for purposes of induced hypotension. Decreased pumping action of the heart, with its resultant fall in cardiac output, does cause a fall in blood pressure. This is probably the mechanism of the hypotension seen with anesthesia of excessive depth regardless of the agent employed. Cardiac output is almost always lowered in induced hypotension, but this decrease is secondary and is never primary by choice.

In clinical practice induced hypotension has been produced mainly by a decrease in the circulating blood volume or by a lowering of the peripheral resistance.

Arteriotomy

Gardner,[62] in 1946, reported on the use of induced hypotension by arteriotomy. Hale[63] described 50 cases done by this technic. He withdrew 1500 to 2000 ml. of blood from the radial artery in a period of thirty minutes. The blood remained outside the body thirty to forty minutes. The average fall in blood pressure was 34 per cent. This fall in blood pressure and the accompanying intense vasoconstriction were reported to decrease blood loss and operative time. Return of the blood from the exogenous reservoir promptly restored blood pressure to normal limits. This form of induced hypotension has not met with wide acceptance or application.

Total Spinal Block

In 1946 Sarnoff and Arrowood[64] demonstrated the principle of "differential spinal block." Their results indicated that sympathetic preganglionic vasomotor fibers could be blocked with a concentration of anesthetic agent less than that needed to impair sensation or motor power. These workers noted a fall in blood pressure with differential sympathetic spinal block similar to that noted after classic spinal block. They concluded from this that the hypotension of spinal anesthesia was primarily caused by blockade of the preganglionic fibers and was not the result of muscular relaxation and diminished thoracic excursion.

In 1948 Griffiths and Gillies[65] described a technic of spinal anesthesia providing both the sensory and muscular paralysis of conventional spinal block and a total blockade of the sympathetic outflow. Thus, surgical anesthesia and profound hypotension were produced without motor paralysis of the higher intercostals or diaphragm. With unremitting attention to a free airway, adequate ventilation with oxygen-enriched mixtures and emphasis on surgical position with the operative site uppermost, they reported a relatively bloodless field without deleterious effects to the patient.

This technic, like all other hypotensive technics based upon a diminution of peripheral resistance, assumes the physiologic premise that adequate oxygenation of the tissues will ensue as long as the hydrostatic pressure at the arterial end of the capillary is sufficient to exceed the sum of the venous pressure combined with the colloid osmotic pressure of the plasma.[66] This pressure at the arterial end of the capillary is considered to be approximately 32 mm. of mercury. In normal blood pressure the rest of the pressure is expended in overcoming the peripheral resistance (chiefly arteriolar).

Ganglionic-Blocking Agents

In 1948 Barlow and Ing[67] and Paton and Zaimis,[68] working independently, synthesized a series of polymethylene bistrimethyl-ammonium salts — the methonium series. Subsequent investigations revealed that decamethonium (C-10) produced neuromuscular block whereas pentamethonium (C-5) and hexamethonium (C-6) prevented the transmission of

impulses across synapses in all autonomic ganglions. The last two compounds, especially hexamethonium, have found extensive clinical use in the production of hypotension.[69-71] Technics for the use of methonium derivatives are accurately described.[69,70] In all cases positioning of the patient is of importance, with the operative site uppermost, the blood pooling in the more dependent portions by gravity.

Another ganglionic-blocking agent, trimethaphan (Arfonad), or d-3,4(1',3'-dibenzyl-2'-keto-imidazolido)-1,2 trimethylene thiophanium d-camphorsulfonate, described in 1949[72] and first used clinically in 1953,[57] is more readily controlled and more quickly reversible than the previously mentioned autonomic-ganglion-blocking drugs. The methonium derivatives are usually given in single or intermittent intravenous doses. Arfonad is given by a continuous intravenous drip. This affords a more flexible and graded lowering of the blood pressure and is usually readily reversible. Blood pressure is regulated by variation of the flow rate. Action of the drug is transient. Slowing or stopping of the infusion returns the blood pressure to normal limits, usually within a few minutes. The hypotension produced by Arfonad as well as by the methonium derivatives may be quickly corrected by the use of a vasopressor drug. These blocking agents have no effect on the action of the various sympathomimetic amines.

Effects of Hypotension on Various Organs

Although hypotensive technics have had extensive clinical trial, there has been a dearth of experimental work on the effects of lowered blood pressure on the brain, kidney, liver and heart of the anesthetized patient. Observers disagree concerning the effects of various anesthetic agents on these organs in the presence of normal arterial blood pressure.[73-77] Results recorded on studies done under hypotension are even more at variance.

Studies on cerebral circulation under the influence of anesthesia and hypotension have dealt mainly with measurements of cerebral blood flow and cerebrovascular resistance. Morris et al.,[78] working with hexamethonium-produced hypotension, found cerebral resistance lowered 11 per cent and cerebral blood flow diminished by 30 per cent. Total cerebral oxygen consumption was decreased only 12 per cent because of the increased extraction of oxygen from arterial blood. Kety and his associates,[79] using differential spinal block in hypertensive patients, described a similar decrease in cerebral blood flow that was attributed to the discrepancy between a considerable fall in mean arterial blood pressure and a slight fall in cerebrovascular resistance. Other investigators have described changes in electroencephalographic and electrocardiographic tracings consistent with hypoxia during hexamethonium hypotension in the head-up position.[80] On the other hand Stone, Mackrell and Wechsler[81] found that an average drop of 44 per cent in mean arterial blood pressure failed to decrease cerebral blood flow or metabolism. Maintenance of cerebral blood flow was attributed to a 46 per cent reduction in cerebrovascular resistance. This work is substantially in agreement with that of Crumpton and Murphy.[82]

Renal blood flow has been found to diminish during hypotension[74,78] although some describe a return of blood flow toward normal after several consecutive hours of hypotension.[78] Miles et al.[83] reported renal blood flow to be largely uninfluenced by a fall in blood pressure. This stability of renal blood flow in the presence of a decrease in blood pressure is possibly due to the property of renal vessels for autoregulation as postulated by Smith and his coworkers.[73]

Lynn et al.[74] found evidence that blood flow to the liver was diminished during hypotension under spinal anesthesia, and Bromage[84] described a local hypoxia of the liver with possible occult liver damage. In contradistinction, the data of Greene and his associates[85] showed equal or less postoperative disturbance in liver-function tests after hypotensive spinal anesthesia as compared with the results after ether or cyclopropane.

It should be noted that all these observations on induced hypotension were not made under uniform conditions. Some of the results were obtained from induced hypotension alone, some from induced hypotension in combination with general anesthesia and some from the use of induced hypotension, general anesthesia and surgery.

Complications

Induced hypotension is not without its complications. Gillies[86] has termed such a technic "physiologic trespass." Hampton and Little,[87,88] in a questionnaire sent to qualified anesthesiologists of Great Britain, Ireland and the United States, collected data on approximately 28,000 cases of induced hypotension under anesthesia. The complication rate reported was 1 in every 31 cases. Some of the complications in descending order of frequency were as follows: reactionary hemorrhage (bleeding from the operative site upon restoration of normal blood pressure); delayed awakening; blurred vision postoperatively; persistent hypotension; anuria, oliguria; cardiovascular collapse; cerebral thrombosis; cardiac arrest; coronary thrombosis; and retinal thrombosis. The mortality in these 28,000 cases was 1 in every 291 patients, a compromise of the circulation of the kidney, brain or heart accounting for more than 50 per cent of the deaths.

It follows from a study of the complications and mortality that a partial list of contraindications to induced hypotension includes generalized arteriosclerosis, cardiac disease, cerebrovascular disease,

renal disease, hepatic disease, the extremes of age and disturbances in blood volume. The data of Hampton and Little indicate that the complications, both fatal and nonfatal, are directly and closely related to the duration and degree of hypotension. The critical level of systolic blood pressure seems to be 80 mm. of mercury. With systolic pressure at or above this level complications are relatively infrequent.

Hypothermia

Virtue[89] defines hypothermia as a state of body temperature below normal in a homeothermic person. Hypothermic anesthesia is defined as analgesia and loss of consciousness due to cold. The use of hypothermic agents in medicine is not new. In 1938 Fay and Henny[90] reported on the local application of cold to malignant lesions. One year later Smith and Fay[91] presented their observations on prolonged general hypothermia for far-advanced cancer. In 1941 Talbott[92] introduced the term "hypothermia" and reviewed the subject up to that time. Crossman et al.,[93] in 1943, described regional chilling for amputation of gangrenous extremities. The application of agents producing hypothermia and hypothermic anesthesia to general surgery, however, can be traced to information obtained from laboratory studies since 1950.

Some of the physiologic effects of cold as determined in the laboratory are briefly and somewhat arbitrarily listed below. In the first place oxygen consumption of the tissues is reduced approximately 5 per cent per 1°C. drop in temperature. At a temperature of 28°C. (82°F.) tissue oxygen requirements are decreased about 50 per cent.[94] Secondly, respirations are progressively slowed as the temperature is lowered. Spontaneous respirations may cease at temperatures of 28°C. (82°F.) and below.[94,95] Thirdly, the pH of arterial blood decreases as the temperature falls and respirations are depressed.[96] Fourthly, blood pressure, heart rate and cardiac output diminish with cooling.[95,97] Fifthly, coronary blood flow and myocardial oxygen consumption decrease; coronary arterial venous oxygen difference remains unchanged from the normothermic state.[98,99] Sixthly, bleeding and clotting times are prolonged.[100] Finally, plasma volumes are diminished.[100,101]

Technic of Administering Hypothermia

Technics for the conduct of hypothermic anesthesia have been described.[89,102-105] With most technics, routine preoperative medication is recommended. Anesthesia is first induced with a general anesthetic, and an endotracheal tube is inserted. Electrocardiographic leads and a thermocouple or rectal thermometer should be in place throughout the entire procedure. The methods used for cooling are relatively simple, such as immersion in ice water, packing in ice and wrapping in refrigerated blankets. Shivering must be controlled to obtain proper cooling. This is accomplished with muscle relaxants or increased depth of anesthesia. Chlorpromazine is thought by some to aid in rapid cooling and the control of shivering.[102,106] The patient is removed from the cooling medium when the temperature has made about 60 per cent of the desired fall. The temperature will continue to drift downward the remaining 40 per cent at a somewhat inconstant rate. At temperatures of about 28 to 30°C. (82 to 86°F.) no further anesthetic drugs are needed. Respirations are controlled, and hyperventilation is instituted. In open-heart surgery, during occlusion of the vena cava, no respiratory movements on the breathing bag are attempted. The cooling process may take from one to three hours. As soon as definitive surgery is finished, rewarming is started. During rewarming, consciousness returns at 32 to 34°C. (90 to 93°F.). The rewarming time varies but is usually about two thirds of the time required for cooling.

Clinical Applications

Intracardiac surgery. The reduced oxygen consumption and diminished metabolic needs of the hypothermic tissues have allowed the heart to be excluded from the general circulation for periods of six to eight minutes without causing irreversible damage to the brain. With these conditions the vena cava can be clamped, and the bloodless heart opened for surgical procedures under direct vision. Lewis and Taufic[107] first reported the successful use of hypothermia for intracardiac surgery on a human patient. They have since presented 11 cases of defect of the atrial septum operated on with the body in a state of hypothermia.[105] Bailey et al.[108] have described 13 patients, 4 of whom underwent an open technic, 1 resulting in the successful closure of a defect of the interventricular septum. Swan and his associates[109] have reported on 100 cases; 59 of these were for intracardiac procedures under direct vision. This series included 12 successful operations for pulmonary valvular stenosis.

Adjunct to conventional surgery. McQuiston[110,111] first reported the use of hypothermia clinically to reduce oxygen requirements in cyanotic children undergoing surgical treatment. Other observers have since agreed with his impression of the beneficial effects of cold in these patients.[106,112,113]

Hypothermia is a potent anesthetic agent in itself. Below 28 to 30°C. (82 to 86°F.) no further drugs are needed. In prolonged procedures and in the presence of severe liver disease cold may be less toxic than some pharmacologic agents. A variety of procedures such as portacaval shunt, abdominoperineal resections and total cystectomies have been performed on poor-risk patients under hypothermia. These patients are reported to have been benefited from a decrease in the metabolic requirements dur-

ing surgery and the lack of anesthetic effects after operation.

In neurosurgery, hypothermia has been induced to lower brain cellular metabolism and allow occlusion of all cerebral circulation for a period without causing irreversible damage. Encouraging results, particularly with aneurysms, have been reported.[115,116]

DeBakey and Cooley[117] and Cooley et al.[118] have used hypothermia for resection of thoracic and aortic aneurysms. These workers believe that the protection afforded the spinal cord and liver by the diminished oxygen tissue requirements during occlusion of the aorta makes resectable virtually all aneurysms of the thoracic aorta located distal to the origin of the left common carotid artery.

Complications

The major and most feared complication of hypothermia is ventricular fibrillation. It may occur at any time during the cooling process with or without occlusion of the circulation. Occlusion of the circulation and manipulation of the heart increases the incidence. The incidence rises sharply with temperatures below 25°C. (77° F.).

Swan and his associates[109] report 22 cases of cardiac arrest (7 of standstill and 15 of ventricular fibrillation) in a series of 100 cases. Lewis, Varco and Taufic[105] described ventricular fibrillation in 4 of 11 cases, and Bailey et al.[108] mention ventricular fibrillation in 8 of 13 cases.

Hyperventilation to induce respiratory alkalosis and decrease the hydrogen ion concentration of the blood is believed by some to reduce the incidence of ventricular fibrillation.[119,120] Electric shock is relatively ineffective in defibrillating the cold heart.[121] Intermittent cardiac compression and immediate rewarming may restore the rhythm to normal. Perfusion of the coronary circulation with a solution of potassium chloride has been reported as effective in defibrillating cold hearts.[109,121] Neostigmine (Prostigmin), administered by coronary perfusion, has also been reported as valuable for defibrillation both experimentally and clinically.[109,122]

Peripheral neuropathies occurred in 12 of 100 cases reported by Swan et al.[109] The cause of these neuropathies is not definitely established. The temperature of the extremities may drop considerably below the temperature recorded rectally. Cold may increase the sensitivity of peripheral nerves to pressure injury.

Other complications include coronary air emboli, hemorrhage after rewarming with return of blood pressure to normal, shock and cardiac dilatation from too rapid return of blood flow to the heart after occlusion.

Chlorpromazine

It was not to be expected that the field of anesthesia would escape an investigation into the applicability of this drug, which has been extensively tried for a variety of conditions.

Reference to the use of chlorpromazine in hypothermia as an aid to cooling and for the control of cardiac arrhythmias has been made.[102,106,114] The value of this drug as an adjuvant to hypothermic anesthesia has been questioned.[123]

Chlorpromazine has been studied as a substitute for premedication.[124-126] In one series, sedation was reported as absent to minimal in over 50 per cent of the cases. Furthermore, induction with inhalation agents was frequently slow and stormy. A drying effect, present subjectively, was not as evident objectively in cases in which a belladonna derivative had been withheld. Hypotension developed in a significant number of patients receiving the drug. This hypotension was more frequent and pronounced with parenteral administration and, once established, often tended to be refractory to the effect of vasopressors given in the usual dosages.

Chlorpromazine seems to potentiate the action of some anesthetic drugs.[127,128] Relatively small doses are effective in potentiating or adding to the potency of preoperative medication and in decreasing the amounts of anesthetic agents required during the surgical procedure. Postanesthetic awakening, however, may be unduly prolonged.

Small intravenous doses of chlorpromazine have been used to control postoperative delirium. Patients tend to return to a deep sleep for an hour or more. Again, hypotension may be present.

The effectiveness of chlorpromazine in the treatment of nausea and vomiting has been reported.[129-131] Whether this drug offers any significant improvement over results obtained with other antiemetics, some of which have considerably fewer side effects, has not been ascertained.

Side effects include the tendency, already mentioned, to produce a hypotension refractory to the usual doses of vasopressors, pain on intramuscular injection, residual soreness at the injection site and jaundice after prolonged administration.

Chlorpromazine does offer considerable promise in the treatment of hiccups both under anesthesia and in patients who are not undergoing operation.[132,133] The routine use of chlorpromazine in anesthesia does not seem to be warranted in view of the lack of definite, demonstrable superiority over other drugs and the presence of frequent undesirable side effects. A possible exception to this generalization is its use in obstetric anesthesia, in which the tranquilizing and antiemetic effects are of great importance.

Hydroxydione (Viadril)

The anesthetic effects of steroid hormones have been recognized for some time.[134,135] Recently, clinical reports on the use of Viadril (21-hydroxypre-

nanedion-sodium-succinate hydroxydione)[136,137] have appeared. The drug is administered intravenously in a 1.0 to 2.5 per cent solution. The usual dose for induction is approximately 500 mg. It is a hypnotic and a weak analgesic agent. It produces an electroencephalographic pattern similar to that of thiopental. Induction is quite prolonged, and may take ten to twenty minutes. The anesthesia usually must be supplemented with some analgesic agent. The solution may be irritating to veins and subcutaneous tissue. Muscle twitchings or spasms of the extremities occasionally occur. Hypotension may follow its rapid administration.

It is not easy to draw the conclusion that this drug has little clinical application at present. It is of interest as a possible precursor to a series of new derivatives.

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MEDICAL INTELLIGENCE

ICHTHYOSIFORM ATROPHY OF THE SKIN IN HODGKIN'S DISEASE*

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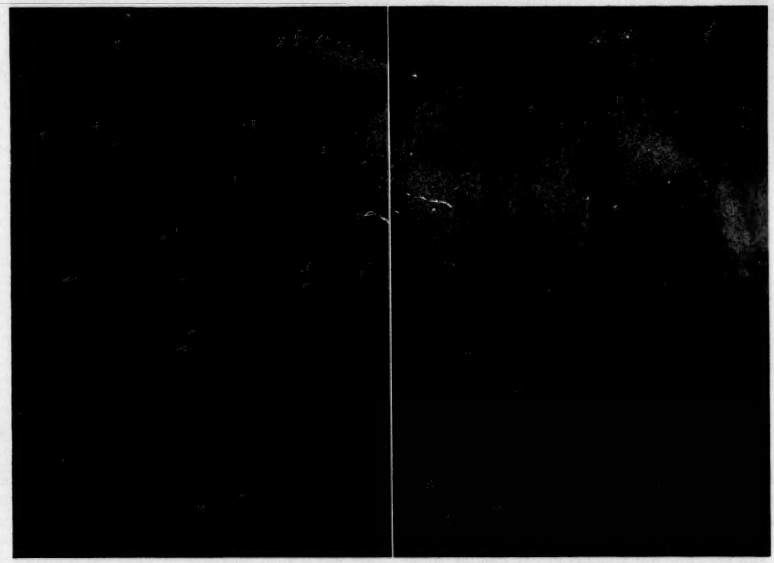
IN 1943 one of us[1] reviewed the literature on the nonspecific cutaneous manifestations described in Hodgkin's disease, and reported a case in a twenty-four-year-old man, who, eleven months before dying from the disease, manifested a dry, wrinkly, hyperpigmented, atrophic skin representing the familiar rhomboidal figuration of acquired ichthyosis, the type commonly called senile ichthyosis because often seen developing in advanced age. Attention was called to this cutaneous nonspecific toxic manifestation of lymphogranulomatosis, perhaps heralding the final stage of the disease. No previous author, as far as we know, mentioned this senile type of ichthyosis occurring as a manifestation of Hodgkin's disease and particularly of aggravation of the disease.

Reiches[2] reported development of ichthyosis four months before death from generalized carcinomatosis. Epstein and MacEachern[3] say that exfoliative erythroderma was the characteristic cutaneous lesion in 66.6 per cent of a series of cases of Hodgkin's disease investigated from hospital records. Nanta and Chatellier[4] spoke of ichthyosiform hyperkeratoses as exceptional cutaneous reactions in Hodgkin's disease. Bluefarb[5] considered ichthyosiform atrophy of the skin in Hodgkin's disease a nonspecific toxic cutaneous manifestation also found in multiple myeloma and lymphosarcoma.



A B

FIGURE 1. *Ichthyosiform Atrophy of the Skin in a Case of Hodgkin's Disease* (A), *Disappearing after X-Ray Therapy and Nitrogen Mustard* (B).

Since the observation of 1943 mentioned above,[1] 10 more cases have been reported. Glazebrook and Tomaszewski[6] presented the case of a fifty-year-old fisherman, who was admitted to the hospital complaining of scaliness of his skin of a few weeks' duration. The entire cutaneous surface became subsequently ichthyosiform. A biopsy of a lymph node showed Hodgkin's disease. The metabolism of vitamin A was

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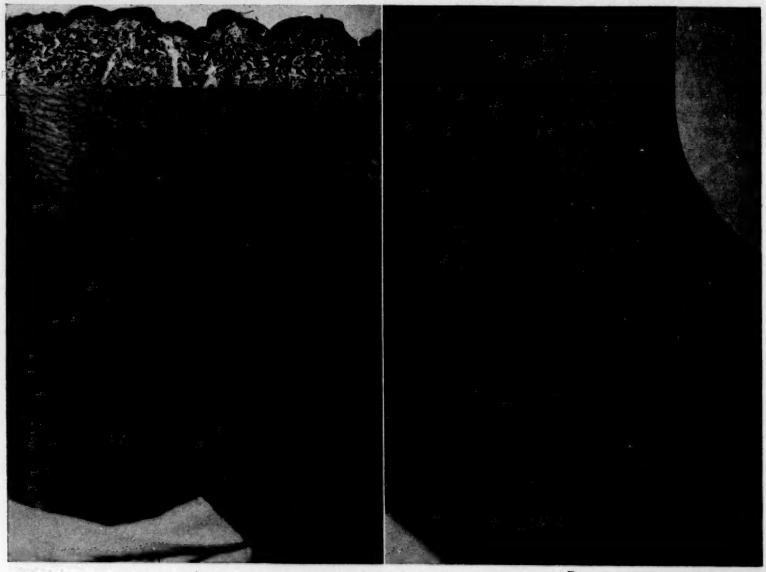
investigated, and the authors suggested that the atrophy may have been a secondary effect of the vitamin A upset. Welch and Epstein[7] reported a case in which ichthyosiform atrophy was the main complaint and led to a diagnosis of lymphoblastoma. Piaggio Blanco and Montero[8] quote a paper by Piaggio Blanco, Pasayro and Sanguinetti with a description of a case in which ichthyosiform atrophy, with the usual clinical and pathological features, appeared six months before any other symptom of



A B

FIGURE 2. *Atrophic, Ichthyosiform Skin, Showing Mild Hyperkeratosis, Thinning and Flattening of the Epidermis and Increased Melanin Pigmentation* (A), *and the Same Area after X-Ray Therapy and Nitrogen Mustard* (B).

Hodgkin's disease. The atrophy disappeared in part after x-ray therapy. Forman[9] presented before the Royal Society of Medicine, Section on Dermatology, the case of a fifty-six-year-old man with ichthyotic skin and enlarged lymph nodes of five months' duration. An excised lymph node showed reticulum-cell sarcoma. In the discussion Vickers[10] stated that he had seen a case of Hodgkin's disease with ichthyosiform dermatitis.

Sneddon[11] reports 4 cases. The first was in a forty-eight-year-old man, ill for five months, who noticed that his skin became dry two months before hospitalization. The skin was indistinguishable from a congenital ichthyosis. A lymph-node biopsy showed Hodgkin's disease, and a skin biopsy hyperkeratosis and atrophy. The patient improved with treatment and then had a recurrence of the disease and the ichthyosis, and both improved with transfusions. The second of Sneddon's cases concerned a fifty-two-year-old man with a history of diarrhea and fatigue and scaly, leafy skin (including the flexures) of five weeks' duration. A tentative diagnosis of Hodgkin's disease was made because of the dryness of the skin. The diagnosis was confirmed at autopsy. The third patient was a sixty-seven-year-old man complaining of eczema for two years. Four months before admission hard, painless lumps appeared on the shoulders and chest. Atrophy of the skin, including the flexures, was noted. This was of recent date. The diagnosis of the nodules was reticulosarcoma, Hodgkin's type. The fourth case was that of an eighty-five-year-old woman complaining of painless lumps on the neck and trunk and mild generalized ichthyosis of recent onset. The pathology was a reticulosis of mycosis-fungoides type.

Boudin, Barbizet and Brion[12] describe the case of a forty-nine-year-old man hospitalized for general weakness, fever and enlargement of the liver, with a skin of striking appearance. The entire cutaneous surface looked like a mosaic, made up of scales the size of a nail. The cutaneous disorder had been present for about one year. Only at autopsy was an

intestinal tumor diagnosed as Hodgkin's disease. The dermatosis was the principal clinical sign.

We wish to report an eleventh case with definite ichthyotic features, consistence and pathology of the skin, in which the peculiar dryness of the skin became more and more apparent with increase in the severity of the symptoms of the disease, and in which the dryness disappeared and the skin returned to apparent normalcy repeatedly as a result of treatment (x-ray therapy and nitrogen mustard).

Case Report

A 50-year-old man, of Italian ancestry, a veteran of World War I, entered the Medical Ward on April 28, 1952, complaining of masses in the right side of the neck of 3 months' and loss of strength and weight of 6 months' duration. The skin was dry, dark and scaly.

A cervical lymph node was removed for microscopical examination, and a diagnosis of malignant lymphoma, Hodgkin-granuloma type, was made. Deep x-ray therapy initiated on May 16 was followed by small elevations of temperature. He received a total of 1250 r to the right side of the neck, and the masses disappeared completely. At discharge on June 18 a change in the texture of the skin was noted, but little importance was attached to this observation at the time.

On the 2d admission, on September 9, the temperature was 102°F., there was further loss of weight, and the patient complained of cough and lumbosacral pain. It was noted that the skin was of a sallow color, nonelastic and wrinkled, with fine and large scales. The right side of the neck was hyperpigmented as a result of the previous x-ray therapy. No lymph nodes were palpable in the neck or anywhere else, but x-ray study disclosed partial destruction of the 3d lumbar vertebra.

The most notable feature, besides the temperature, the pain and the general weakness, was the ichthyosiform atrophy of the entire skin (Fig. 1*A*) and the rhomboidal scales usually seen as a permanent feature in the so-called senile ichthyosis. The distribution was on the entire body, including the flexures and creases. The patient ran daily elevations of temperature as high as 103°F. Because of low hemoglobin (8.6 gm. per 100 ml.) transfusions were given for 5 days. A total of 2000 r was given to the lumbar spine, followed by nitrogen mustard in dosages of 5.5 mg. daily for 4 days, a total of 22 mg. The temperature fell to normal; the white-cell count went from 6800 to 1800. When discharged on October 24, the patient had gained 5.9 kg. (13 pounds) in weight and was feeling generally well. A most remarkable change was noted in his skin (Fig. 1*B*), which had returned practically to a normal color, appearance and consistence.

He was readmitted to the hospital for the 3d time on January 19, 1953, with the same symptoms: high temperature, fatigue, loss of weight and marked ichthyosiform atrophy of the entire skin (Fig. 2*A*). This time clinical photographs were taken, and a biopsy performed. This showed a heavy horny layer, all the other layers being thin, and the papillae flat. No evidence of lymphogranulomatosis was found. He received transfusions and the same course of nitrogen mustard therapy, which resulted in increase in weight, a sense of well-being and return of the skin to normal, as after the previous course of treatment (Fig. 2*B*). A repetition of the same course of events occurred at the time of the 4th admission, between April 27 and June 11, 1953, and after the 5th admission, from December 14, 1954, to January 21, 1955. The same ichthyosiform skin was observed. He again received blood transfusions and nitrogen mustard, followed by deep x-ray therapy. As previously, he improved immediately; his appetite returned, he gained weight, and the skin returned to a normal appearance.

Summary and Conclusions

An ichthyosiform atrophy, of the senile ichthyosis type, developed in the skin of a man suffering from Hodgkin's disease.

The skin returned to an apparently normal appearance and consistence after x-ray and nitrogen mustard therapy, together with an increase in weight and general well-being.

This change from atrophy to normal and vice versa was observed in five admissions and discharges.

This is the eleventh case of this kind so far reported.

Even if such a manifestation is apparently nonspecific, Hodgkin's disease, or a disease of the lymphoma group, should be remembered when one is presented with a case of sudden change of texture of the skin from normal to ichthyosiform.

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THYROID FUNCTION IN LEGG–PERTHES DISEASE

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CORRIGAN and his associates[1] reported that of 35 patients with Legg–Perthes disease studied by their methods none had normal thyroid function. It has long been suspected that some relation existed between Legg–Perthes disease (aseptic necrosis of the head of the femur) and thyroid function, but previously no one could establish evidence of a significant alteration of thyroid function in such patients. Several years ago Albright[2] called attention to the fact that changes simulating Legg–Perthes disease could occur in the epiphyses of many bones during juvenile myxedema. Likewise, Jackson, Hanelin and Albright[3] emphasized the fact that a single roentgenogram of one epiphysis (hip) in multiple epiphyseal dysplasia may resemble the changes

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seen in cretinism, Morquio's disease or Legg–Perthes disease.

In a further search for the truth in this matter, 10 children with Legg–Perthes disease were examined especially for evidence of thyroid disease. A carefully taken history was included, and physical examination of each child was done at the New England Peabody Home for Crippled Children. Then, the forty-eight-hour uptake of radioactive iodine by the thyroid gland was measured at the Thyroid Laboratory of the Massachusetts General Hospital, and blood drawn for the determination of the serum protein-bound iodine. It is believed that these tests are the most informative laboratory indexes of thyroid function.

It is evident from the data in Table 1 that with these methods of study, no evidence of thyroid dysfunction could be discovered in 5 girls and 5 boys with Legg–Perthes disease. The interesting physiologic feature of the data is the remarkable uniformity of the thyroid avidity for radioactive iodine, and the similarity of the measurable serum protein-bound iodine. These patients live under identical conditions of activity, clothing and diet. In support of these findings, clinicians over the past twenty-two years found no evidence of thyroid disease in the 65 patients (14 girls and 51 boys) with Legg–Perthes disease treated at the New England Peabody Home; 1 patient did have pan-hypopituitarism with hypothyroidism as part of the syndrome, and yet the course of his Legg–Perthes disease seemed unaltered by thyroid, 120 mg., administered daily for four of the six years he was in the home.

TABLE 1. *Thyroid-Function Studies in Legg–Perthes Disease.*

PATIENT	HOSPITAL NO.	SEX	BIRTH DATE	THYROID GLAND	48-HR. UPTAKE OF I^{131}*	SERUM PROTEIN-BOUND IODINE†	TOTAL IODINE	IODIDE IN 24-HR. URINE SPECIMEN	LOCATION OF LESION	DURATION OF DISEASE	COMMENT
					%	*microgm./ 100 ml.*	*microgm./ 100 ml.*	*microgm./ 100 ml.*			
P.de B.	849	F	8-1-46	Normal	29	5.6	5.7	105	Left hip	2 yr.	Mother always limped
J.F.D.	863	F	1-25-47	Normal	29	4.1	4.5		Left hip	1 yr.	Mother had hyperthyroidism
J.S.H.	867	F	11-9-43	Normal	32	5.1	6.7		Left hip	1 yr.	
L.M.F.	878	F	6-11-45	Normal	35	6.6	7.6	167	Left hip	1 yr.	Obese mother & father
L.A.P.‡	884	F	3-25-51	Normal	33	4.7	4.7		Both hips	6 mo.	
D.A.P.‡	876	M	4-1-47	Normal	32	4.9	5.9	149	Right hip	1 yr.	
S.W.T.	868	M	6-18-46	Normal	33	4.8	6.6	110	Right hip	18 mo.	
T.S., Jr.‡	871	M	11-7-47	Normal	32	5.2	7.0		Left hip	10 mo.	
J.T.C.	844	M	7-6-43	Normal	33	5.3	5.6		Left hip	2½ yr.	Father, paternal uncle & grandmother had Legg–Perthes disease
R.R.W.‡	881	M	5-7-49	Normal	29	5.5	6.4		Left hip	10 mo.	

*Accepted normal values, 25 to 52%.
†Normal values, 4 to 8 microgm./100 ml.
‡In active phase of disease.

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CURRENT CONCEPTS IN THERAPY*

SULFONAMIDES

ALTHOUGH the newer antibiotics have replaced the sulfonamides in the treatment of many infections the sulfonamides are still of great value in therapy. Used wisely, they have much to offer and are frequently the agents of choice. Since they are easily synthesized they can be produced in large quantities at little cost, and, consequently, they are the most economical of the drugs used to combat infection.

The sulfonamides in the usual blood-stream concentrations are bacteriostatic agents that restrain growth of bacteria, thus permitting normal phagocytic and immune processes to clear up the infections. When concentrated at high levels, as in the urine, they can have a bactericidal effect. Although not supported by some facts, the theory that the sulfon-

*Prepared under the supervision of the *Journal's* Committee on Advertising.

amides act by interference with the utilization of para-aminobenzoic acid by the organism explains many of the observed data.[1] Sulfonamide resistance appears not uncommonly and certainly more frequently in infections that have not been eradicated by two weeks of therapy. This resistance may be of two types. A rapidly appearing and readily lost resistance is produced when variation by enzyme adaptation occurs, and a more slowly developed and usually permanent resistance results from variation by selection in which the resultant organisms are different enzymatically from the parent. If resistance is to be avoided, infections must be cleared promptly, and this is best done by maintaining adequate blood levels at all times.[2]

After absorption the sulfonamides readily diffuse into all body fluids, including the cerebrospinal fluid, where levels of 50 per cent or more of the blood level are easily attained. They are then either acetylated, combined with serum protein, or excreted unchanged. The degree of acetylation and protein combination varies with the preparation and the level of the drug in the blood stream. Most acetylated forms are less soluble in the urine and are a hazard to the genitourinary tract unless adequate urinary flow, 1500 ml. or more daily, is maintained and highly acid urines avoided. Consequently, such a preparation as a mixture of three sulfonamides, which is highly effective and yet, owing to the individual solubility of the acetyl derivative, has minimum potentiality for crystalluria, is highly satisfactory.[3]

Excretion is by the kidney and therefore is dependent on good renal function and an intact genitourinary tract. In the presence of renal impairment dangerous levels of the sulfonamides can readily occur.

Prescribed wisely a sulfonamide offers no more hazard than any other potent agent. Some toxic reaction will develop in approximately 5 per cent of patients. These consist of the less severe effects of nausea, vomiting, fever, headache and dizziness, or the more serious effects of damage to the kidneys, with hematuria, oliguria or anuria, skin rash, anemia, leukopenia, or agranulocytosis and hepatic or widespread vascular damage.

The sulfonamides are very useful against many infections and may be the treatment of choice in meningococcal infections and some bacillary dysenteries. They may be adequate for uncomplicated pneumococcal and streptococcal infections and some infections of the urinary tract. Alone or in combination with antibiotics, they may be helpful in the treatment of infections caused by streptococci, staphylococci, pneumococci, meningococci, gonococci, colon bacilli, anthrax, shigella, cholera, *Haemophilus influenzae* and brucella. They are also helpful against infections caused by large viruses, such as granuloma inguinale, lymphopathia venereum, ornithosis and psittacosis. They are of limited value against infections due to *Aerobacter aerogenes,* proteus, *Pseudomonas aeruginosa,* clostridia and *Pasteurella tularensis.*

Although over 5000 sulfonamides have been synthesized, therapeutic needs are adequately covered by a few readily absorbed, systemic-acting preparations. Sulfadiazine may be used alone, in combination with sulfamerazine and sulfamethazine, or with sulfamerazine and sulfacetamide. Others that have been shown to be useful include sulfacetamide, sulfisoxazol (Gantrisin) and those acting locally in the bowel, succinylsulfathiazole (Sulfasuxidine) and phthalylsulfathiazole (Sulfathalidine). Mafenide (Sulfamylon) is a unique sulfonamide that is commonly used topically since it is active even in the presence of pus, whereas the other common ones are not.

Sulfonamides should be given in sufficient amount to maintain an adequate blood level — usually, about 10 mg. per 100 ml. is satisfactory. A level that is too low may hasten the development of resistance and give a poor effect, whereas a level that is too high is more likely to have a toxic effect. Usually, an initial dose of 4 to 6 gm. of sulfadiazine or triple sulfonamides followed by 1 gm. every four hours gives excellent results: larger amounts of sulfisoxazol may be used, generally 1.5 gm. every four hours. Since the kidney concentrates these agents ten to twenty times, excellent results are frequently obtained in the treatment of urinary-tract infections with a dose of 2 gm. every twelve hours. Succinylsulfathiazole and phthalylsulfathiazole administered for local intestinal effect should be given in a dose of 3 gm. three or four times a day.

The topical use of sulfacetamide as a 30 per cent solution or 10 per cent ointment for susceptible infections of the eye is very useful. Mafenide (Sulfamylon), as a 5 per cent solution, is effective applied topically in otitis, sinusitis and other infections of the mucous membrane or cutaneous lesions.

There is little or no merit to the routine administration of combinations of sulfonamides with other antibiotics. Best results with the sulfonamides, as with other agents, can only be obtained by the proper adjustment of dose. When indicated, penicillin or other antibiotics may be given concurrently with excellent effect. Topical applications, except as indicated above, are usually undesirable.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42321

PRESENTATION OF CASE

First admission. A thirty-three-year-old laborer entered the hospital because of joint pains.

Thirteen years previously episodes of external dyspnea and palpitation were noted. One year later painful swelling and limitation of motion of the joints of the extremities occurred. With rest the swelling and pain subsided, and there was return of full motion. Joint symptoms recurred one year and four years later. Slight exertional dyspnea continued. During the two years before entry there were episodes of sudden severe pain in the sacroiliac region and intermittent painful swelling of the ankle joints. The last severe exacerbation occurred four months before admission.

He was said to have had rheumatic fever with painful joints for several months when he was three and chorea when he was eight years of age.

Physical examination showed a well nourished man who complained of pain with movement of the lower back. There was tenderness over the lumbosacral joints. Both ankles were swollen and tender. The heart was not enlarged. The pulmonic second sound was louder than the aortic. A Grade 1, apical systolic and a Grade 2 diastolic murmur that was loudest along the left sternal border, especially in the third intercostal space, were audible. Examination of the lungs and abdomen was negative. There was no edema.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 50 to 30 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 14 gm. per 100 ml. and a white-cell count of 7400. The sedimentation rate ranged between 0.60 and 0.82 mm. per minute. X-ray films of the chest showed straightening of the upper left cardiac border, most pronounced posteriorly in the left anterior oblique view; the heart was not enlarged, and no intracardiac calcification was observed; the aorta and lungs were normal. Films of the spine demonstrated sclerotic changes about both sacroiliac articulations, with widening and irregularity of their margins inferiorly. X-ray films of the ankle joints showed no characteristic changes. An electrocardiogram revealed a normal rhythm at a rate of 70; the PR interval was 0.22 second; the T waves were upright in Leads 1 and 2 and isoelectric in Lead 3; the P waves were split in Leads 1 and 2.

With the use of a plaster shell the back pain was relieved. About a week before discharge there was a transitory episode of swelling of the sternoclavicular joints.

The patient was discharged improved on the forty-second hospital day.

Second admission (twelve years later). Several months after discharge, because of recurrent painful swelling of the ankles and pain in the back as well as stiffness and aching of the left fourth finger, salicylate therapy was given, with improvement. There was also an episode of acute uveitis on the right. Subsequently, there continued to be exacerbations and remissions of pain in the joints. A year later intramuscular gold therapy was given, with improvement in joint symptoms. Because of the occurrence of a maculopapular skin rash and leukopenia the gold was discontinued. The sedimentation rate ranged between 0.43 and 1.00 mm. per minute. An electrocardiogram nineteen months after discharge showed a normal rhythm at a rate of 80, with a rare ventricular premature beat; the PR interval was 0.18 second; the axis was normal; the T waves were upright in Leads 1, 2 and 3; the P waves were low and indistinct in Leads 2 and 3. An x-ray film of the right foot five months later showed minor degenerative changes of the tarsal bones; an ill defined spur was seen arising from the base of the os calcis.

Nine years before entry physical examination revealed the cardiac impulse to be at the anterior axillary line in the sixth left intercostal space. A loud, blowing, diastolic murmur, loudest at the apex, was audible over the precordium; the aortic second sound was absent and replaced by the murmur. There was a moderate amount of lower thoracic kyphosis that could not be corrected by attempted extension of the spine. X-ray films of the chest demonstrated some evidence of left ventricular hypertrophy. Because of constant, severe, throbbing pain in the mid-thoracic spine, aching in the lower back and an occasional twinge of pain in the left ankle, salicylate therapy was continued with barbiturates, and a plaster cast for the back was again used. There was improvement with this regimen. The sedimentation rate ranged between 0.26 and 0.68 mm. per minute. Six months later x-ray films of the spine showed the sacroiliac joints to be narrower than usual; they were irregular

in their inferior half and exhibited increased density; the smaller joints of the lower lumbar spine appeared slightly narrower than usual; there was narrowing of the intervertebral disk between the twelfth dorsal and first lumbar vertebras, with bridging of these two vertebras and some degenerative changes of the second and third lumbar vertebras. Four months later slight exertional dyspnea associated with some malaise and occasional ankle edema occurred. There continued to be episodes of joint pain. The spine remained rigid, and there was pain in the upper dorsal spine. In addition to the previously noted cardiac murmurs one observer heard a very soft mitral diastolic rumble. The blood pressure was 146 systolic, 40 diastolic. Because of a slight increase in exertional dyspnea associated with malaise and occasional ankle edema, salt intake was restricted, and digitalis administered. The sedimentation rate ranged between 0.27 and 0.44 mm. per minute.

Six and a half years before admission an electrocardiogram showed a normal sinus rhythm with ventricular premature beats; the axis was +30°; the PR interval was 0.37 second; the T waves were upright in Leads 1, 2, aVL and V_2 through V_4, low in Leads aVF and V_5 and diphasic in Leads 3 and V_6; the ST segments were slightly elevated in Lead aVL and sagging in Leads V_5 and V_6; there were deep S waves in Lead V_2 and high R waves in Leads V_5 and V_6. The patient continued to have moderate joint pains as well as some exertional dyspnea and palpitations. Digitalis was discontinued. The sedimentation rate ranged between 0.32 and 0.65 mm. per minute.

Four months before entry there was a progressive increase in exertional dyspnea, with palpitation and increased fatigability. Two months later there began to be episodes of pain in the left side of the chest, with radiation down the left arm. These attacks were associated with exertional dyspnea and sometimes with weakness and sweating. The pain was relieved by rest. Orthopnea was noted, and, for two weeks before admission, there were episodes of wheezing and coughing up of blood-tinged sputum, associated with pleuritic pain in the left side of the chest and axilla, as well as paroxysmal nocturnal dyspnea.

Physical examination showed a dyspneic man who appeared chronically ill. The veins of the neck were distended and pulsating. Examination of the lungs showed diffuse wheezes and rales, especially at the left-lung base. The heart was enlarged, and the cardiac sounds were difficult to hear because of the pulmonary wheezes. The apical systolic and aortic diastolic murmurs were the same as previously noted. The liver edge, which was nontender, was just palpable at the costal margin. There was no edema. Marked limitation of motion in the lumbar and thoracic spine was noted.

The temperature was 99.2°F., the pulse 92, and the respirations 20. The blood pressure was 135 systolic, 65 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 14.7 gm. per 100 ml. and a white-cell count of 8400. The sedimentation rate was 7 mm. per hour (Wintrobe method). The nonprotein nitrogen, the total protein, the albumin, the globulin and the fasting blood sugar were normal. The sodium was 130 milliequiv., the potassium 4.5 milliequiv., the chloride 89 milliequiv., and the carbon dioxide 29 milliequiv. per liter. The blood Hinton test was negative. X-ray films of the chest showed cardiac enlargement that was seen fluoroscopically to involve the left atrium and ventricle, moderate pulmonary vascular congestion, some fluid in both pleural cavities and two linear areas of increased density near the left leaf of the diaphragm. An electrocardiogram showed a normal sinus rhythm at a rate of 75; the PR and QRS intervals were 0.28 and 0.16 seconds, respectively; there were slurring and notching of the QRS interval in Leads V_5 and V_6; very deep S waves in Leads V_1 through V_3, and tall R waves in Leads V_5 and V_6. A phonocardiogram showed no apparent first sound, a second sound of low intensity, a systolic murmur of low intensity and a presystolic murmur of moderate intensity at the apex; at the pulmonic area there was a delayed first sound and a widely split second sound followed by a diastolic murmur that was best registered at the left sternal border but was seen in all areas. Culture of the throat grew out abundant alpha-hemolytic streptococci and moderate *Neisseria catarrhalis*. Cytologic examination of the sputum for malignant cells was unsatisfactory and negative.

With digitalis and Mercuhydrin therapy the patient improved and was discharged on the ninth hospital day on digitalis, acetyl salicylic acid and a low-sodium diet.

Final admission (eight months later). In the interval he felt well until six weeks before entry, when increasing exertional dyspnea was noted. Three weeks later there was a sudden onset of sharp pleuritic pain in the left side of the chest. He began to have a cough productive of mucoid sputum, which six days before admission was blood tinged. For three days before entry the exertional dyspnea worsened, and there was frequent paroxysmal nocturnal dyspnea as well as ankle edema. On the day before admission, in addition to the pain in the chest, there was a dull, steady pain over the epigastrium and middle portion of the abdomen. On the day of admission numbness in the right side of the face was noted, and the right side of the mouth appeared to droop. Shortly afterward he suddenly felt dizzy and became cyanotic and unresponsive. With oxygen therapy he became responsive, and his color improved.

Physical examination revealed a slightly dyspneic man with a marked malar flush. The neck veins were distended when he was raised to an angle of 45°. The carotid pulses were bounding. Examination of the chest showed dullness, with diminished

breath sounds and moist rales at the left-lung base. In addition to previous findings, examination of the heart revealed a Grade 3 apical diastolic rumble with an obscured second sound. The edge of the liver was palpable 3 fingerbreadths below the costal margin. There was + + pitting edema of the legs.

The temperature was 99.4°F., the pulse 134, and the respirations 28. The blood pressure was 120 systolic, 70 diastolic.

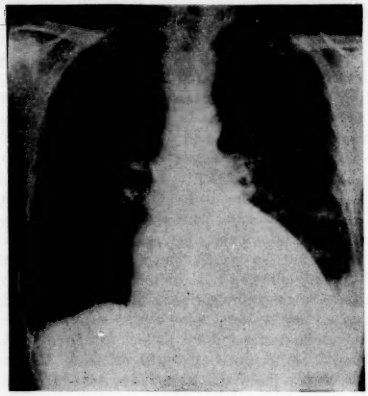

FIGURE 1.

The urine gave a + test for albumin. Examination of the blood revealed a hemoglobin of 14.2 gm. per 100 ml. and a white-cell count of 8500. The nonprotein nitrogen was 55 mg. per 100 ml. The sodium, potassium and chloride were normal. X-ray films of the chest demonstrated fluid in the left pleural space, elevation of the left leaf of the diaphragm and a patchy linear density in the left lower lobe (Fig. 1), with some reduction in the size of this lobe. An electrocardiogram showed a supraventricular tachycardia at a rate of 110; the QRS and QT intervals were 0.18 and 0.40 seconds, respectively; P waves were not seen; the QRS segment was depressed in Lead V_1 and elevated in Lead V_6; the ST segment and T waves were directed opposite to the main deflection of the QRS waves.

On the second hospital day a bilateral superficial-femoral-vein ligation was performed; no thrombi were found. The abdominal pain subsided, and there was an occasional sharp pleuritic pain in the anterior portion of the left side of the chest. The patient was found dead on the second postoperative day.

DIFFERENTIAL DIAGNOSIS

DR. GORDON S. MYERS*: I think we should first look at the x-ray films of the chest.

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DR. C. C. WANG: In the roentgenograms taken nearly thirteen years before the final admission the lung fields are clear, and the heart is not enlarged. From then on there is continuous progressive cardiac enlargement, which primarily involves the left ventricle and to a slight degree the left atrium. The aorta is normal in size. The films made during the last admission show in addition a few linear, patchy densities in the left lower lobe and some fluid in the pleural cavities, more on the left side (Fig. 1). There is no evidence of intracardiac calcification.

DR. MYERS: Is there any calcification of the ascending aorta?

DR. WANG: There is none that I can detect in the films.

DR. MYERS: In the film taken at the time of the first admission, do you think that the left atrium is enlarged?

DR. WANG: No.

DR. MYERS: Are there other views of the heart?

DR. WANG: There is a lateral projection, but it is not helpful. Films of the lumbar spine and pelvis show considerable decalcification of the bone and slight herniation of the disk into the first lumbar vertebra. There is definite evidence of sclerosis and narrowing of the sacroiliac joints.

DR. MYERS: Are those changes consistent with rheumatoid arthritis?

DR. WANG: Yes.

DR. MYERS: Do you think that the findings in the last film of the chest are compatible with pulmonary infarction on the left?

DR. WANG: Yes.

DR. MYERS: I think that I am uncomfortably ensconced on the horns of a dilemma, because this case seems to come down to a question of rheumatoid heart disease or rheumatic heart disease or perhaps both. One thing seems clear: this patient had aortic regurgitation of important degree. I have no good reason for diagnosing syphilitic heart disease, healed bacterial endocarditis or traumatic rupture of the aortic valve. It is most unlikely that this will prove to be any form of congenital lesion, such as bicuspid aortic valve with regurgitation. The patient evidently had rheumatoid arthritis. Certainly, the history, including an episode of uveitis, and the x-ray appearance of the joints indicate that diagnosis.

Patients with rheumatoid arthritis may have aortitis that produces aortic regurgitation. The rheumatoid process may also involve the myocardium, causing prolongation of the PR interval and widening of the QRS complexes; it sometimes involves the pericardium, causing pericardial effusions. Patients who have rheumatoid aortitis with aortic regurgitation are usually males and ordinarily suffer from spondylitis, as this patient did. Aortic regurgitation that becomes increasingly free can give rise to an Austin-Flint murmur simulating mitral stenosis. The

slight systolic murmur at the apex could have been caused by dilatation of the left ventricle, with functional mitral regurgitation. Finally, patients who have rheumatoid aortitis with aortic regurgitation may die of congestive heart failure. Nothing about this patient would exclude the diagnosis, but there are some troublesome features. In the first place there was a history of rheumatic fever in childhood: he had not only joint trouble but chorea. Furthermore, he had arthritis and dyspnea for thirteen years before the first admission, and yet at the time of the first admission the heart was not particularly large, if large at all. It would be odd for a patient to carry on for twenty-five years after the onset of dyspnea before dying of congestive heart failure if the symptoms were due to aortic-valve disease. One is tempted to think of mitral stenosis even in the absence of a mitral diastolic murmur. Sometimes, the murmur may not be heard even though stenosis is marked.

It is most important under these circumstances to have a careful evaluation of the patient's complaint of dyspnea. Was he a nervous person with sighing respirations typical of neurocirculatory asthenia? Was there any indication that the dyspnea was caused by asthma or by restriction in vital capacity secondary to the arthritis? It would be interesting to know what the vital capacity was.

Dr. Paul D. White has said that in following patients with fairly free aortic regurgitation due to rheumatic heart disease, a few have shown a decrease in aortic regurgitation because of increasing aortic stenosis. That might explain the increase in diastolic blood pressure in this patient during later admissions to the hospital; however, no aortic systolic murmur was heard to indicate aortic stenosis. The apparent rise in diastolic pressure took place at times when the pulse rate was increased. An increase in the pulse rate can give rise to an apparent increase in diastolic pressure in patients with aortic regurgitation, the increased rate resulting in a shorter diastolic period and less actual regurgitation of blood into the left ventricle with each heart beat.

I come now to the phonocardiogram in trying to decide between rheumatic and rheumatoid heart disease. It is difficult to understand how one can hear a first heart sound at the base over the pulmonic area and not hear it at the apex. The phonocardiographers, one of whom is here today, say the first heart sound usually has four components — the first being atrial, and the second being caused by closure of the atrioventricular valves, the third by opening of the aortic and pulmonic valves, and the final component by the expulsion of blood from the ventricle into the arteries. In mitral stenosis the phonocardiogram frequently records a delay in the appearance of the first heart sound — really the second component of the first heart sound — after the onset of the QRS complex in the electrocardiogram. I believe that the theory is that there is a high gradient of pressure in diastole between the left atrium and the left ventricle that is maintained throughout the diastolic period in such a way that the valve leaflets are held in a more inward position than usual so that after the onset of ventricular systole it takes longer than usual for the valves to close. Such timing of the first sound in a patient with mitral stenosis, who is fibrillating, varies according to the preceding cycle length — that is, the longer the cycle length, the less the delay. In the patient under discussion there was no first sound at the apex. What a delayed first sound in the pulmonic area means I do not know; but I do not think that it is strong evidence in favor of mitral stenosis. In fact, the absence of a first sound at the apex, even in the presence of a long PR interval (which tends to make the first sound less apparent), seems to be some evidence against mitral stenosis. Furthermore, no opening snap was recorded, and there was no evidence of calcification of the mitral valve in the x-ray films.

The two final events — the severe pain in the left side of the chest and the blood spitting — suggest pulmonary infarcts, especially in a patient who was in congestive heart failure. I suppose he could have had pneumonitis or atelectasis, but I think pulmonary infarcts more likely. I am sure that the Service believed this to be the case, for the leg veins were tied. The episode of weakness and numbness of the right side of the face could have been caused by a small cerebral embolus or thrombosis. Very little else is said in the protocol except that these symptoms cleared up rapidly. I do not know how to evaluate the symptoms.

For my final diagnosis I shall select rheumatoid arthritis with rheumatoid involvement of the aorta and free aortic regurgitation without disease of the mitral valve. I certainly cannot exclude the possibility of rheumatic heart disease or of both rheumatic and rheumatoid heart disease together. I am sure that the patient was in congestive heart failure. I suppose that he had pulmonary infarcts of the base of the left lung and perhaps a small cerebral infarct.

DR. BENJAMIN CASTLEMAN: Dr. Sprague, will you comment on Dr. Myers's discussion?

DR. HOWARD B. SPRAGUE: I do not recollect that I saw the patient, although I am told that he was on my Service a year or so ago. Would you read me the diagnosis when he was discharged?

DR. CASTLEMAN: "Rheumatoid arthritis, spondylitis, rheumatic heart disease with aortic regurgitation, mitral regurgitation and stenosis and ? aortic stenosis — H. B. Sprague."

DR. SPRAGUE: I am in the same dilemma in which Dr. Myers was. A possible explanation for the delayed first sound at the base is that it may have been the "early systolic sound" that occurs with dilatation of either the aorta or the pulmonary artery — presumably, the patient had aortic dilatation. It is

thought to be the result of expansion of the vessel at the onset of ventricular ejection.

About the so-called group diseases, I have been impressed that not only is this a group of diseases but that the group is often grouped in the type of patient who is discussed at these conferences. The pathologist may find not one but two or more of the so-called group diseases in one patient. Two may have been present in the patient under discussion.

DR. CASTLEMAN: Dr. Bland, what is your opinion?

DR. EDWARD F. BLAND: Of these two experts, one has chosen rheumatic heart disease, and the other rheumatoid heart disease.

I favor slightly rheumatic heart disease. I am resistant to the concept of "free" aortic regurgitation, with a diastolic pressure of 70. In our experience the patients with free aortic regurgitation have usually had diastolic pressures of 40 to 30 down to 0. A point in favor of Dr. Myers's diagnosis is the patient's dying suddenly in bed at night. That is usually the fate of patients with free aortic regurgitation, after the onset of heart failure or angina pectoris decubitus.

DR. CASTLEMAN: How large should a heart with free aortic regurgitation be?

DR. BLAND: I think it should weigh about 1000 gm. From the x-ray appearance I doubt if this patient's heart weighed over 600 gm.

DR. MYERS: About six months ago I saw with Dr. Reed Harwood a patient who had syphilitic aortitis, with aortic regurgitation. He had pulmonary edema. I continually measured the diastolic pressure in that patient at 60 to 70. I made the comment in the record that this was disturbing. However, when the congestive heart failure was controlled and the heart rate came down, the diastolic pressure dropped to about 20. This makes sense from a hemodynamic standpoint, since one should expect a rise in diastolic blood pressure if the pulse rate is rapid.

DR. BLAND: I am sure that that is true. Conversely, rheumatic children with free aortic regurgitation and a diastolic pressure of 30, when they have vascular crises, usually have no measurable diastolic pressure.

DR. MARIAN W. ROPES: Over the many years we were impaled on the horns of the same dilemma many times. I am sure there was no consensus in our group about the diagnosis. During the first few years we thought that this patient had rheumatic heart disease associated with rheumatoid arthritis. Toward the end there was a change of opinion. I thought that rheumatoid heart disease was more likely because of the increasing evidence of spinal involvement, the uveitis and all the other signs that so commonly occur in this group of patients. I believed that the dyspnea early in the history of this over-reactive man was difficult to interpret. He had no dyspnea later, and between attacks of failure he did heavy labor. The periods of incapacitation that appeared suddenly seemed out of proportion to the organic disease.

DR. BLAND: I suppose that subacute bacterial endocarditis was ruled out carefully at the end.

DR. JACOB LERMAN: Dr. Myers, if there was cerebral embolus, where do you think it arose?

DR. MYERS: Ordinarily, one would expect that only in a patient who was fibrillating; on the other hand, we do occasionally see peripheral emboli in patients who are not recognizably fibrillating but may have paroxysms of fibrillations when not under observation.

DR. LERMAN: From the atrium?

DR. MYERS: We are never sure of that.

DR. LERMAN: Would that argue for mitral stenosis?

DR. MYERS: Not strongly enough for me to change my diagnosis.

DR. CASTLEMAN: Do you think that this patient had mitral stenosis, Dr. Lerman?

DR. LERMAN: On that basis, I should say that he had mitral stenosis.

CLINICAL DIAGNOSES

? Rheumatoid heart disease, with aortic regurgitation.
Pulmonary infarcts.

DR. GORDON S. MYERS'S DIAGNOSES

Rheumatoid aortitis, with aortic regurgitation.
Rheumatoid arthritis.
Congestive heart failure.
Pulmonary infarcts, left base.

ANATOMICAL DIAGNOSES

Rheumatoid aortitis, with aortic regurgitation.
Cardiac hypertrophy and dilatation, marked (970 gm.).
Hydrothorax, left.
Pulmonary congestion.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The heart weighed 970 gm. There was marked flattening of the left ventricle, which one would expect with severe aortic regurgitation. There was no disease of the mitral valve. The aortic valve was distorted: the cusps were rolled and pulled downward, leaving a large space between the edges of the cusps and the aortic wall. There may have been a little interadherence at the commissure, but no real separation. Above the aortic cusp there was a change in the intima, but only for a short distance; immediately above this area of change the aorta was perfectly normal (Fig. 2). The change consisted of plaquelike thickening of the intima and, in a few spots, calcification. This appearance is the

one we see often in syphilitic aortitis as well as in rheumatoid aortitis.

In microscopical sections through the aorta, the intima was thickened and the media was diseased with areas of necrosis — so-called necrobiosis — and an inflammatory reaction around the vasa vasorum. The vessels in the adventitia were very thick — a finding characteristic of this condition. A stain for elastic tissue revealed spotty areas of absence of elastica, which were replaced by fibrosis and necrosis.

FIGURE 2.

I believe that this is the seventh case that has come to autopsy out of a series of 18 or 19 in which a diagnosis of a rheumatoid aortitis has been made clinically. This material is being studied by Dr. Richard J. Clark and Dr. Peter S. Kulka at the present time.

DR. SPRAGUE: Was there any change in the myocardium?

DR. CASTLEMAN: In the myocardium there were some areas of falling out of myocardial fibers, but there were no inflammatory changes, no Aschoff bodies and no rheumatoid nodules, which we occasionally see in the myocardium or pericardium.

The left pleural cavity contained 1200 ml. of fluid. There was marked chronic passive congestion of the lungs, but no infarcts and no emboli. The brain was normal.

DR. BLAND: I think that it is fair to say that this form of heart disease is a Massachusetts General Hospital entity. The first case was recognized here in 1936 and carefully studied by Dr. Mallory.[1,2] The sections were shown to the late Dr. A. M. Pappenheimer in New York, who had never seen anything just like it. Two weeks ago I had the pleasure of spending several days with Dr. Paul Klemperer at a meeting in Mexico; he probably knows more about the pathology of collagen diseases than anyone else. We discussed this special form of heart disease. He remembered that Dr. Pappenheimer had shown him the original sections and that he had thought they resembled mostly an acute syphilitic process. He said that since then he has not seen a single case.

DR. CASTLEMAN: We are certain that it is not syphilis. All the cases have been studied carefully for syphilis. The original slides were sent to Dr. Pappenheimer because he had reported cases of rheumatic aortitis, which looked quite different from this condition.

DR. ROPES: We are now doing *Treponema pallidum* immobilization tests on patients with this condition, in the hope of ruling out syphilis more conclusively.

DR. CASTLEMAN: There is a report[3] of 5 cases of this condition, 2 with post-mortem examinations, in a recent issue of the *New England Journal of Medicine*.

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CASE 42322

PRESENTATION OF CASE

A seventy-nine-year-old man entered the hospital because of jaundice.

Five or six weeks previously dark urine was noted several times. Ten days before admission he had epigastric distress after a heavy meal. A stool was passed "explosively" three hours after he took milk of magnesia. Subsequently, there was persistent anorexia. Dark urine was again passed during the ten days before entry. Four days before admission his physician noted that he was jaundiced. The evening before entry he became nauseated and vomited a recently ingested meal. Except for a vaguely described "lameness" along both costal margins that did not radiate, there had been no pain. There was a recent loss of 10 pounds in weight. There were no chills, fever or clay-colored stools. There had been no change in bowel habits.

Thirteen years previously a transurethral resection for benign prostatic hyperplasia and fulguration of a carcinoma of the urinary bladder with implantation of radon seeds was done. Except for a brief episode of hematuria ten years later there were no subsequent signs or symptoms of urinary-tract disease. Stilbestrol therapy had been given after the episode of hematuria. Bilateral inguinal herniorrhaphies were performed three years before admission.

Physical examination showed a well nourished, deeply jaundiced man. Gynecomastia on the right was noted. There was no lymphadenopathy. Examination of the heart revealed Grade 2 to 3 apical and basal systolic murmurs. There was moderate, diffuse, deep abdominal tenderness with rebound tenderness. The liver edge, which was firm and tender, was felt 2 fingerbreadths below the right costal margin. A palpable, tender gall bladder was noted by one observer. The spleen was not felt. The testes were atrophic. Rectal examination revealed a slightly enlarged, irregular, hard, nontender prostate.

The temperature was 98°F., the pulse 70, and the respirations 20. The blood pressure was 120 systolic, 75 diastolic.

The urine, which was deeply bile stained, gave a ++++ test for albumin; the sediment contained numerous white cells, bacteria and hyaline and granular casts; a culture gave a moderate growth of nonhemolytic streptococci, a few *Bacillus pyocyaneus* and abundant coliform bacilli. Examination of the blood revealed a hemoglobin of 11.6 gm. per 100 ml. and a white-cell count of 9700. The nonprotein nitrogen was 33 mg., the total protein 5.3 gm., the bilirubin 15.2 mg., and the fasting blood sugar 62 mg. and 78 mg. per 100 ml. The sodium was 136 milliequiv., and the potassium 4 milliequiv. per liter. The prothrombin content was 11 per cent, and the cephalin flocculation ++++ in twenty-four hours. The alkaline phosphatase was 5.7 units. The amylase was 7 Russell units. The blood Hinton test was negative. A stool specimen, which was dark brown and liquid, gave a negative guaiac test. X-ray films of the chest were normal except for moderate pulmonary emphysema. An abdominal film demonstrated involvement of the right half of the pelvis and the proximal portion of the right femur by Paget's disease; a small metallic density was seen within the bony pelvis; there was a small bit of calcification opposite the right renal pelvis. An upper gastrointestinal series showed delay in gastric emptying thought to be probably the results of pressure upon the junction of the first and second portions of the duodenum; the superior aspect of the proximal portion of the duodenum was indented; the duodenal loop was slightly widened, and there was irregularity of its medial aspect inferiorly. An electrocardiogram was normal.

On the third hospital day it was noted that during in postmenopausal women, but I have never seen a lethargic and disoriented. He gradually became semistuporous, and fibrillary twitchings of the muscles of the arms and chest were noted. A lumbar puncture on the next day yielded 6 ml. of clear, acellular xanthochromic cerebrospinal fluid under an initial pressure equivalent to 120 mm. of water and a final pressure equivalent to 90 mm.; the total protein was 45 mg. per 100 ml. The blood ammonia was 126 microgm. per 100 ml. The prothrombin content was less than 10 per cent. Treatment consisted of bed rest, one blood transfusion, Mephyton (vitamin K_1) and fluids given intravenously. The abdominal tenderness persisted and was most marked in the right upper and lower quadrants. There was some spasm on the right, with inconstant rebound tenderness. Increasing abdominal distention and absence of peristaltic sounds were noted. The patient's course was rapidly downhill with deepening jaundice and coma. An abdominal paracentesis on the sixth hospital day yielded 50 ml. of clear, yellow fluid; cytologic examination for malignant cells was negative. The temperature ranged between normal and 99.6°F. He died on the seventh hospital day. Terminally the white-cell count was 16,500, and the hemoglobin 14.8 gm. per 100 ml.

Differential Diagnosis

Dr. Gerald S. Foster*: This seventy-nine-year-old man had epigastric distress and anorexia followed by progressive jaundice, rapidly became comatose and died — all within a seventeen-day period. The striking features, therefore, appear to be the progressive and intense jaundice and the fulminating course.

Clay-colored stools were not noted before admission to the hospital. A stool specimen on admission to the hospital was described as dark brown. The alkaline phosphatase was only minimally elevated. These features, in the face of progressive jaundice, should rule out extrahepatic obstruction as the primary cause and lead me to turn my attention to the liver. There was a ++++ cephalin flocculation, a low serum total protein value, a markedly depressed prothrombin concentration, apparently in spite of treatment with vitamin K_1 intravenously, and an elevated blood ammonia level. These features indicate severe hepatocellular disease as the cause of the jaundice, and it seems reasonable to conclude that the illness was on the basis of some sort of fulminating hepatic coma and death.

At this point it might be well to review the x-ray films.

Dr. Joseph Hanelin: Review of the films from the gastrointestinal examination shows variable narrowing at the junction of the first and second portions of the duodenum. This finding is not persistent, as shown in various spot films. Similarly, the indentation upon the second portion of the duodenum is

*Assistant in medicine, Massachusetts General Hospital.

not sufficiently constant for me to be certain that a true abnormal pressure deformity exists. There does not appear to be any obvious intrinsic disease of the stomach. The lungs are unremarkable except for the moderate degree of emphysema, and there is indication of Paget's disease of the right hemipelvis and proximal femur.

DR. FOSTER: The films are not too helpful. Whether or not the distortions in the vicinity of the duodenum are significant is difficult to say. Carcinoma of the head of the pancreas or of the ampulla, metastatic lymph nodes in the area and biliary-tract disease with secondary adhesions all might produce such a distortion and might lead to jaundice. However, the jaundice under such circumstances would be of the obstructive type, so that I am forced to turn my attention to other considerations.

Could this man have had cirrhosis? This history here is incomplete. It would be important to know something about the previous alcoholic intake and the general state of his health before the onset of illness. On admission he was described as well nourished, and there was no ascites, splenomegaly or spider angiomas. It would have been helpful to have a film of the esophagus along with the gastrointestinal series to see if varices were present. The gynecomastia and testicular atrophy are difficult to evaluate in view of the age of the patient and the previous stilbestrol therapy. Evidence for any serious degree of cirrhosis, therefore, seems to be lacking; even if there was some degree of latent chronic liver disease, I think one would have to postulate that something else transpired to explain the sudden fulminating course.

Could this have been on the basis of some circulatory disturbance such as is seen with acute thrombosis of the hepatic veins? This commonly results in a fulminating course, but the usual picture is one of a rapidly enlarging liver and ascites, with minimal if any jaundice, so that I think that this is an unlikely explanation.

Neoplastic disease of the liver must always be considered when jaundice appears in this age group. Metastatic disease is the commonest form. The patient had a cancer of the bladder fulgurated thirteen years before admission and had a brief episode of hematuria three years before admission. Metastases of a bladder carcinoma usually occur slowly and almost always extend locally. It would be unusual for a cancer of the bladder to give extensive metastases to the liver without first becoming more manifest locally. Stilbestrol therapy was given for a time three years before admission after the episode of hematuria, and on physical examination at this time he was found to have a slightly enlarged, irregular, hard, nontender prostate. It is possible that he had a cancer of the prostate. However, there were no signs of any bony metastases, and it would be unusual for metastatic disease from the prostate to manifest itself in this way. Carcinoma of the pancreas with extensive metastases to the liver is another possibility. However, metastatic lesions to the liver, whatever the primary site, usually do not run such a fulminating course; jaundice is usually not very intense unless extrahepatic obstruction is a factor, which does not seem to have been the case here; and laboratory studies do not usually show such severe functional impairment. Nevertheless, I cannot rule out extensive hepatic metastases.

Primary carcinoma of the liver must always be considered in any patient presenting evidence of hepatic damage and a rapidly downhill course. Preexisting cirrhosis is usually the case, and here evidence for it seems to be lacking. One would also expect some fever and possibly a larger, harder liver. However, as with metastatic disease to the liver, this possibility cannot be ruled out.

A severe toxic hepatitis due to chemicals or drugs should be considered in any fulminating case of liver disease, and the history should be taken carefully with this in mind. The protocol made no mention of such an exposure, so that I shall assume that this can be ruled out.

The last category of liver disease that should be considered is infection. Pyogenic infection may reach the liver via the bile ducts, portal veins or hepatic arteries. The bile ducts usually are the route when there are cholecystitis, gallstones and an ascending cholangitis; the portal veins, when there is intra-abdominal sepsis—often appendicitis; and the hepatic arteries, when there is infection elsewhere in the body. A tender gall bladder was noted by one observer. During the course of the illness the patient exhibited tenderness both in the upper and lower quadrant on the right side, with increasing distention and ileus. There was also evidence for pyelonephritis, which could have been a source of blood-borne infection. However, under these circumstances jaundice is usually mild unless there is an associated cholangitis, when the jaundice is of the obstructive type. Furthermore, spiking fever, chills and leukocytosis are characteristic and were notably absent in this case. The abdominal fluid obtained was not purulent. I believe that pyogenic abscesses of the liver are therefore quite unlikely and think that the pyelonephritis was a coincidental finding. Miliary tuberculosis and Weil's disease might also be mentioned under this category, but seem quite unlikely.

Finally, we are left with a fulminating viral hepatitis leading to acute necrosis of the liver. The onset of the disease with epigastric distress and persistent anorexia, the progressive jaundice, the laboratory tests indicating severe hepatocellular disease and the fulminating course with changes in the state of consciousness, fibrillary twitchings and finally coma and death are all consistent with such a diagnosis. The age of the patient is, of course, the major drawback. Fulminating hepatitis has occasionally been reported in postmenopausal women, but I have never seen a

case occurring in a man of this age. Nevertheless, I believe that this must remain a consideration.

In summary, this seventy-nine-year-old man had an acute fulminating illness characterized by progressive jaundice, with evidence of severe hepatocellular disease and with rapid progression into hepatic coma and death. Of the considerations mentioned above I am left with either an unusually fulminating case of extensive neoplastic disease of the liver or a severe viral hepatitis. The comment in the protocol that dark urine was noted five or six weeks previously may be a clue in this regard. I am going to assume that this meant bile in the urine and indicated that the process was probably present at that time. This would be a rather long "preicteric" phase for severe hepatitis so that I am going to choose an extensive malignant process as my diagnosis. In the absence of good evidence for cirrhosis I find it difficult to diagnose a hepatoma, so that this must be metastatic disease, and I should guess that the primary tumor was in the pancreas.

DR. LEONARD ATKINS: Dr. Barnes, will you tell us the opinion on the ward?

DR. BENJAMIN A. BARNES: This patient presented to those in immediate attendance a bizarre and confusing picture, with deepening jaundice overshadowed by a rapid deterioration in the state of consciousness. Simple extrahepatic biliary-tract obstruction seemed unlikely because of the precipitous decline in his condition, and on the ward we favored carcinoma of the pancreas, with widespread metastases. He was being prepared for exploration to exclude definitely an extrahepatic block when his condition became so critical as to contraindicate any surgical intervention.

CLINICAL DIAGNOSIS

Carcinoma of pancreas, with widespread metastases.

DR. GERALD S. FOSTER'S DIAGNOSIS

Carcinoma of pancreas, with metastases to liver.

ANATOMICAL DIAGNOSES

Acute fulminant hepatitis with atrophy, probably viral, ? toxic.

Cholelithiasis and choledocholithiasis with intrahepatic calculi.

PATHOLOGICAL DISCUSSION

DR. ATKINS: At autopsy the significant findings were in the liver and biliary tract. The liver was markedly diminished in size, weighing 600 gm.; it was soft and yellow tan. The common bile duct, the hepatic ducts and the intrahepatic bile ducts were slightly distended. Black, friable, facetted calculi measuring up to 0.5 cm. in diameter were found impacted in the ampulla of Vater, which appeared completely obstructed. Similar calculi were present in the gall bladder and intrahepatic and cystic ducts. The pancreas was normal.

Microscopically, there was extensive confluent centrilobular necrosis of the liver, with remaining islands of hepatic cells in the portal areas (Fig. 1). Different stages of necrosis from complete loss of liver cells to variable degrees of fatty vacuolization were present. Regeneration was not a prominent feature. Numerous bile "thrombi" were present in the biliary canaliculi. There was hemorrhage and an inflammatory reaction that consisted of numerous polymorphonuclear leukocytes and a lesser number of mononuclear cells throughout the liver.

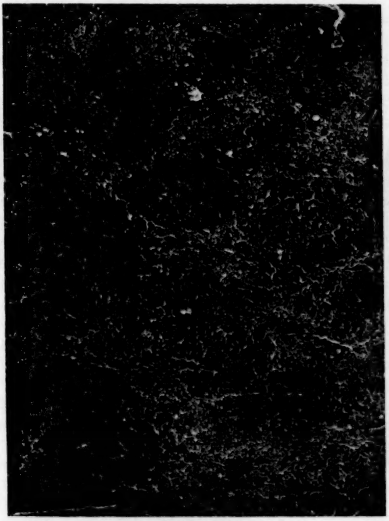

FIGURE 1.

One wonders whether this process was the result of a "toxic" hepatitis although there was no known exposure to a hepatotoxin in this case. It therefore appears more likely to have been an acute viral hepatitis. The dark urine noted five or six weeks before admission was probably related to temporary complete obstruction of the common bile duct by calculi. The prostate showed benign hyperplasia. No evidence of residual tumor was found in the urinary bladder.

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EQUINE ENCEPHALOMYELITIS IN MASSACHUSETTS

CASES of encephalitis due to specific viruses other than those of mumps and poliomyelitis are rarely diagnosed in New England. Two papers appearing in this issue of the *Journal*, each reporting 2 cases of encephalomyelitis that were proved to be caused by the virus of eastern equine encephalomyelitis are therefore of special interest. The virus was isolated from the brain in the only fatal case among the 4, whereas the etiologic diagnosis was established serologically in the other 3 cases. The fatal case was in an infant; 1 of the others was also in an infant, who has remained unconscious and in a vegetative state for more than six months. The remaining 2 cases were in adults in the fifth decade of life; both have recovered, apparently without sequelae.

These 4 cases occurred between mid-September and the second week in October, 1955, during the waning phase of the severest epidemic of poliomyelitis ever to occur in eastern Massachusetts. The 4 patients all lived within a radius of 15 miles of Boston. The source of the infection in the present cases was not definitely established. However, as in the only other previously recognized occurrence of this disease in human beings in this area in 1938, encephalomyelitis due to the same virus was prevalent and highly fatal among horses in several Massachusetts communities, notably in the southeastern part of the State.

The epidemiology of the disease is reviewed in these papers. It is clear that the exact mode of transmission from wild birds or from diseased horses is by no means clear. Nor are the conditions necessary for the epizootic occurrence in horses understood, but the disease has apparently occurred sporadically in horses in Massachusetts in almost every year since it was first recognized here in 1938. During the outbreak of that year the importance of mosquito vectors was stressed. However, Holden,* in studies made among commercially raised pheasants in New Jersey, recently demonstrated that such arthropod vectors are not essential for the transmission of infection with this virus. Moreover, it has often been pointed out that the occurrence of cases in late September and in October, as in the cases reported here, is not entirely consistent with mosquito transmission.

From the clinical point of view the knowledge of the occurrence of fatal encephalomyelitis in horses within several miles of a human case of encephalitis should alert one to the possibility of this specific diagnosis. In the present outbreak it is not unlikely that other cases, particularly fatal ones, occurred and were mistakenly diagnosed as poliomyelitis. The specific diagnosis may be readily established, as in the present cases, by viral isolation or serologically. Unfortunately, treatment is only symptomatic in either disease, since

*Holden, P. Transmission of eastern equine encephalomyelitis in ring-necked pheasants. *Proc. Soc. Exper. Biol. & Med.* **88**:607-610, 1955.

specific therapy is not available. Immunization against eastern equine encephalomyelitis, as pointed out by Winters, is not at present a practical or hopeful procedure.

MORE HEALTH FOR MORE MONEY

THE Congress of the United States, the most generous benefactor in the history of this or any other recognized world, has appropriated for the seven National Institutes of Health for the fiscal year the tidy sum of $170,400,000. This appropriation, some 80 per cent more than was allotted to the seven scientific sisters of the year that ended on June 30, 1956, must be spent before July 1, 1957. Not only will the institutes then have far more money to spend than ever before, according to the Washington Office of the American Medical Association, but presumably far more than their directors had dared hope for when hearings on their budgets commenced last winter.

Without apparent reference as yet to the recommendations of the Long Committee of the National Science Foundation that the system of categorical grants to extramural institutions be overhauled, the bulk of the appropriation will go to non-federal establishments such as hospitals, medical schools, clinics and state and local organizations engaged in research, on a basis of disease categories. Thus, research in cancer will receive $48,400,000, or $23,600,000 more than was received last year and $16,000,000 more than was requested in January when the budgets went to Congress. Mental health will receive $35,100,000 — $17,100,000 more than last year and $13,400,000 more than was requested; heart disease is allocated $33,300,000, compared with $18,700,000 last year and the $22,100,000 that was requested, and so on down the line. Arthritis and metabolic diseases will receive a boost of $5,100,000, bringing their total to $15,800,000, neurology and blindness $18,600,000 compared with last year's allocation of $9,800,000 and a request of $12,100,000, and allergies and infectious diseases are upped from $7,500,000 to $13,200,000. Dental research, with an insignificant appropriation of $6,000,000, will nevertheless receive nearly three times the paltry $2,100,000 that was granted to it last year.

In addition the allocation to the Hill–Burton program has been raised by $14,100,000, and vocational rehabilitation by $2,700,000; states assistance will increase by $600,000, and Indian health work, a previous blot on the escutcheon, will go from $34,700,000 to $38,000,000. Nor will the Veterans Administration suffer in the clamor for more knowledge regardless of the cost. Its own "broader attack upon the 'unknown' in man's major diseases" will be started immediately with its current appropriation of $10,000,000 — $4,300,000 more than was received last year.

It may be hoped that there is no hidden fallacy in the nation's attitude toward money and what it can accomplish; that this country, so capable and yet so capable of being fatuous, is not drifting through a fiscal dream state. But perhaps history has at last reversed itself and prosperity has become both automatic and permanent.

FURTHER OBSERVATIONS ON MATRIMONY

AGAIN the perseverant statisticians of the Metropolitan Life Insurance Company, in a report issued appropriately before June had reached its close, announced good tidings pertaining to those domestic relations associated with the state of matrimony.

Marriage, according to the Metropolitan's matrimonial investigations, is on the upgrade, the total number of married persons in the country's population having reached the record number of 81,750,000 as compared with 75,000,000 in 1950 and 60,250,000 in 1940. Matrimony may be assumed to bear some relation to rises in population, preferably preceding them by a decent interval, and this seems to be the case with the statistics so recently analyzed.

At the beginning of the current summer nearly 70 per cent of the population of the United States fifteen years of age or over was married; little more than 60 per cent was similarly related during the decades prior to the second world war.

The greater part of the relative increase in double blessedness is the result of early marriage; contributing factors are the decrease in mortality in early and middle adult life, with a postponement of widowhood, and a high remarriage rate among those who have lost their partners by death or due process of law. The trend toward earlier marriage has been observed since the turn of the century and has reached the point where the proportion of married men between twenty and twenty-four years of age increased from 27 per cent in 1940 to 51 per cent in 1955. At the moment approximately half the men who marry do so before the age of twenty-three, whereas the median age for first marriages among women is twenty.

The Cesarean section was recently successfully performed in Richmond, Va., by Dr. Charles S. Mills, on a negro dwarf, 3 feet 9 inches in height — both mother and child doing well. The operation, it is said, has never before been successfully performed in that State.

Boston M. & S. J. *August 14, 1856*

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Ovarian Cystadenoma, with Metastases

A twenty-seven-year-old gravida I had no gynecologic complaints before pregnancy. Pelvic examination is said to have been negative early in pregnancy, which was uneventful until the twenty-eighth week, when she was hospitalized after fainting at work. She complained of pressure pains, marked dyspnea and constipation. Examination of the blood revealed a red-cell count of 3,100,000, with a hemoglobin of 8.1 gm. per 100 ml., and a white-cell count of 11,000. She was discharged four days later with a diagnosis of "anemia of pregnancy." An iron-and-vitamin preparation was prescribed. Because of dyspnea, digitalis was given, but without relief. No pelvic examination was recorded.

For the next six weeks she did poorly at home and was taken to the hospital by ambulance with severe abdominal pain and distention. Shortness of breath had increased. She had lost weight. Constipation had increased, with no bowel movement in the past forty-eight hours. She appeared acutely ill, markedly dehydrated and emaciated. She was too weak to talk. There was a right-sided hydrothorax. A mass was palpable in the left lower quadrant separate from the uterus, which was thought to be consistent with a seven-and-a-half-month pregnancy. The fetal heart beat was present. On admission the hemoglobin was 14 gm. per 100 ml., and the white-cell count 13,000. The nonprotein nitrogen was 71 mg., and the uric acid 10.5 mg. per 100 ml. Thoracentesis yielded 3200 ml. of blood-tinged fluid. On the following day, a consultant on pelvic examination found a firm, irregular mass filling the cul-de-sac and left vault. Intestinal drainage, antibiotics, intravenous infusion of fluids and vitamins were instituted, but only 100 ml. of urine was excreted in spite of an intake of 3000 ml. in twenty-four hours. During the next seventy-two hours azotemia increased, and the patient's general condition deteriorated. Since the consultant believed that the baby stood a fair chance of survival, a cesarean section was done four days after the second admission. A normal infant, weighing about 1.3 kg. (3 pounds), was delivered, and survived. An obvious ovarian carcinoma replaced both ovaries, obliterated the cul-de-sac and extended up both gutters, forming a mass as large as the pregnant uterus. Multiple peritoneal and hepatic implants were present. Postoperatively the systolic blood pressure was maintained with difficulty by transfusion and nor-epinephrine at levels never exceeding 80 mm. of mercury. The patient died with continued anuria in profound shock thirty-six hours after delivery.

This case was classified as a nonpreventable death from cystadenocarcinoma of the ovary with metastases. This woman undoubtedly would have succumbed regardless of treatment, but certain aspects warrant further comment.

She was sick enough to require hospitalization during the twenty-eighth week of pregnancy, but only secondary anemia was discovered. One wonders whether a pelvic examination was done at this time. It seems obvious that a mass would undoubtedly have been apparent, even allowing for subsequent rapid growth to its ultimate size in six weeks. Transfusion could have been considered and, at the very least, more intensive antianemic therapy than was given. Mere curiosity would have called for further study. The use of digitalis for dyspnea without heart disease is open to serious question. In other words, the ovarian carcinoma could have and should have been diagnosed at the time of the initial admission. If it had been, surgical excision of the parent tumor and the larger metastases could have been performed, as well as any other treatment that might have seemed indicated. Certainly, delay of radiation in the interest of the fetus might have been warranted, but the mother's outlook could have been vastly improved surgically at the twenty-eighth week, and her life more comfortably prolonged. One suspects that careful prenatal supervision, with repeated examinations because of her poor condition, might have diagnosed the carcinoma well in advance of that time.

It is a tribute to the surgeon that he was able to extricate a living infant, and it is a further tribute to the nursery that this child survived.

John Figgis Jewett, M.D.
Chairman

THE ORIGINAL CHARTER

For many years a copy of the original charter of the Massachusetts Medical Society, dated 1781, has been carefully preserved in a metal case in the safe at 8 Fenway.

It has recently been discovered that this is only an amanuensis copy of the original document. The actual charter was found in the custody of the Archives Division at the State House. It is written on vellum, faded and somewhat damaged. It bears the signatures of John Hancock and many other notable persons.

Arrangements have been made to reproduce the original vellum charter by the collotype process. The Meriden Gravure Company has informed us that the value of such collotype prints is at least $5, and

that reproductions of similar quality are sold at double this price in print shops.

Only a few reproductions will be made. They will be made available to all fellows of the Society who wish to purchase one, at a cost of no more than $5 and perhaps less.

Requests should be addressed to the Secretary.

ROBERT W. BUCK, M.D.
Secretary

NONCLINICAL NOTES

NEW ENGLAND ROENTGEN RAY SOCIETY

The New England Roentgen Ray Society recently elected the following officers for the year 1956-1957: president, Dr. Leslie K. Sycamore, Hanover, New Hampshire; vice-president, Dr. Harvey R. Morrison, Boston; secretary, Dr. Raymond A. Dillon, Winchester, Massachusetts; and treasurer, Dr. Magnus I. Smedal, Boston.

NOTICES

INTERNATIONAL COLLEGE OF SURGEONS

The Twenty-first Annual Congress of the United States and Canadian Sections, International College of Surgeons, will be held in the Palmer House, Chicago, Illinois, September 9 through 13. The International House of Delegates will meet on the morning of the opening day, Sunday, September 9. In the afternoon, the House of Delegates, United States Section, will convene for the biannual election of officers and for other business. The Canadian Section will hold a business meeting Monday afternoon and a dinner in the evening. Further information may be obtained from the Secretariat, International College of Surgeons, 1516 Lake Shore Drive, Chicago 10, Illinois.

NEW HAMPSHIRE AND VERMONT STATE MEDICAL SOCIETIES

The 1956 Joint Meeting of the New Hampshire and Vermont State Medical societies will be held at Wentworth-by-the-Sea, Portsmouth, New Hampshire, on October 7, 8 and 9. Reservation cards will be sent out by both state society executive offices about July 1. The Vermont and New Hampshire Heart associations will hold joint meetings, with Dr. Paul Dudley White as a featured speaker.

NEW YORK ACADEMY OF MEDICINE

The Twenty-ninth Annual Graduate Fortnight of the New York Academy of Medicine will be held at the Academy, October 15 through 26. The subject will be on "Selected Subjects of Current Significance." Reports on five general topics of special current importance will be presented, reducing the total number of fortnight sessions. A series of three lectures will be presented at a single session on five alternate evenings, and panel meetings and clinicopathological conferences on five alternate afternoons. Throughout the fortnight there will be a scientific exhibit on display. Further information may be obtained from Dr. Robert L. Craig, Secretary, Graduate Fortnight Committee, New York Academy of Medicine, 2 East 103 Street, New York 29, New York.

LIFE INSURANCE MEDICAL RESEARCH FUND

The Life Insurance Medical Research Fund announces that applications for postdoctoral research fellowships (stipend, $3,600) will be accepted until October 15, 1956. Preference is given to those working on cardiovascular function and disease or related fundamental problems. Awards will be available on July 1, 1957.

Applications for grants to institutions for aid in research on cardiovascular problems will be received until November 1, 1956. Support is available for physiologic, biochemical and other basic work broadly related to cardiovascular problems and also for clinical work in this field.

Further information may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, New York.

SOCIETY MEETINGS AND CONFERENCES

AUGUST 19-23. American College of Chest Physicians. Page 840, issue of November 10.
AUGUST 24 and 25. National Hemophilia Foundation. Page 249, issue of August 2.
AUGUST 27 and 28. Consultation Clinics for Crippled Children in Massachusetts. Page 1244, issue of June 28.
SEPTEMBER 3-5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 3-7. First Inter-American Conference on Occupational Medicine and Toxicology. Page 152, issue of July 19.
OCTOBER 8-13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 16

THURSDAY, AUGUST 16
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. The Embryologic Basis of Congenital Heart Defects. Dr. Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, AUGUST 17
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, AUGUST 18
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

(Concluded on page xxx)